

The increased prevalence of allergic disease in anhidrotic congenital ectodermal dysplasia

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Anhidrotic congenital ectodermal dysplasia (ACED) is a sex-linked recessive disorder which is characterized by anodontia or severe hypodontia, anhidrosis or severe hypohidrosis, and hypotrichosis. Afflicted individuals may also demonstrate evidence of hypoplastic changes in the respiratory mucosa. Seven male patients with ACED were found to have a statistically significant increased prevalence of extrinsic bronchial asthma and/or allergic rhinitis and an increased prevalence of positive prick test reactions to common inhalant allergens when compared with a control population examined in the Tecumseh Community Health Study. Four patients with ACED and allergic disease had no consistent abnormality in serum IgG, IgA, or IgM levels, and both transport piece and IgA were demonstrable in their salivary secretions or parotid fluid. It is postulated that the increased prevalence of allergic disease in patients with ACED may be due to an abnormality of the nasal mucosa resulting in an increased permeability to or decreased destruction of inhaled allergens.

The anhidrotic form of congenital ectodermal dysplasia (ACED) is a rare hereditary disorder characterized by the triad of anhidrosis or severe hypohidrosis, anodontia or severe hypodontia, and hypotrichosis.¹⁻³ The disorder was first described by Thurnam⁴ in 1848 and was more fully characterized by Weech⁵ in 1929. Skin biopsies from afflicted individuals demonstrate an absence of eccrine sweat glands, producing an inability to regulate body temperature in warm weather. The disease often presents in infancy as recurrent bouts of

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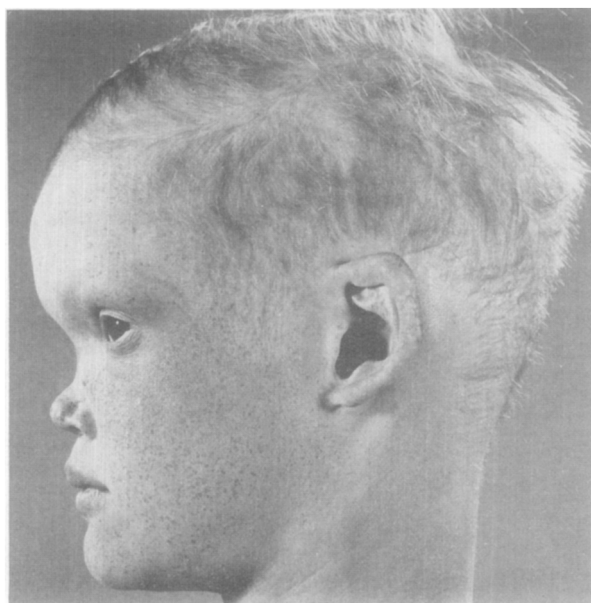


Fig. 1

Patient K. H. Note the prominent frontal bossa, saddle nose, abnormal external ears, and sparse eyebrows and scalp hair.

unexplained fever. The anodontia or hypodontia affects both the deciduous and permanent teeth. Some teeth fail to erupt while others are grossly deformed, peg shaped, or conical in appearance. The third feature, hypotrichosis, presents clinically as sparse, fine, blond scalp hair, absent eyebrows and eyelashes, and absent or scant body, axillary, and pubic hair. Individuals with ACED have a typical facies (Fig. 1) characterized by prominent frontal bossae, prominent supraorbital ridges, saddle-nose deformity, anomalies of the external ears, and protruding lips.

A number of other abnormalities have been reported in most patients with ACED. These include: hypoplasia or absence of the mammary glands; diminished lacrimal function; smooth, thin dry skin; and dystrophic nail changes. Of particular interest is the frequent occurrence of hypoplastic changes in the mucosa and mucus-secreting glands of the nose, pharynx, and larynx, resulting in a chronic atrophic rhinitis with foul nasal discharge, destruction of the nasal septum, and varying degrees of hoarseness.¹⁻³

ACED is inherited as an X-linked recessive disorder. Over 90 per cent of cases occur in males. Female carriers may demonstrate subtle dental abnormalities, fine hair, and a patchy decrease in sweating which can be demonstrated only with the use of special techniques.

ACED must be distinguished from the hidrotic form of ectodermal dysplasia in which abnormalities of the hair and teeth occur in the presence of normal sweating.² The latter is inherited as an autosomal dominant. ACED must also be distinguished from mesoectodermal dysplasia and chondroectodermal dysplasia

(Ellis-Van Creveld syndrome) which differ from it in both their clinical features and mode of inheritance.¹

Recently we had an opportunity to examine 2 unrelated patients with classical ACED who also had flexural eczema and respiratory allergy. This stimulated our interest in the possibility of an association between ACED and allergic disease and led to the present study.

SUBJECTS AND METHODS

Subjects

Seven patients with classical ACED form the basis of this report. All were examined as part of a joint study of ACED conducted by the Department of Pediatrics and School of Dentistry of The University of Michigan. The 2 patients initially seen in our allergy clinic were included, but their entrance into the study had been arranged prior to the time our interest was expressed. All 7 were males from different kindreds, ranging in age from 2 to 32 with a mean of 14 years. Each had unequivocal evidence of anodontia or severe hypodontia, anhidrosis or marked hypohidrosis, and hypotrichosis. Varying degrees of atrophic rhinitis were present in the patients as evidenced by a dry crusted nasal mucosa with or without purulent nasal discharge.

Methods

A complete history and physical examination, including allergy history and an environmental survey, were performed on each patient. Prick tests were done with the following standard skin test materials from the University of Michigan Allergy Clinic: elm, oak, box elder, orchard grass, timothy, dwarf ragweed, giant ragweed, *Alternaria*, *Hormodendron*, University of Michigan stock house dust, Endo house dust,* milk, wheat, egg, and saline control. The preparation of these extracts⁶ and criteria used for reading the tests on a negative to 4+ scale⁷ have been described previously. In our experience, false positive "irritant" reactions are seldom encountered when prick tests are performed with these extracts.

Quantitative serum immunoglobulin determinations⁸ for IgG, IgA, and IgM were performed with the use of commercially available Hyland Plates.† Passive transfer studies for determination of ragweed reagin titers were done by the standard Prausnitz-Küstner (P-K) technique. The results were averaged from duplicate runs of serially diluted serum. In all instances duplicate determinations were within a single twofold dilution of each other.

Fifty milliliters of parotid fluid was collected from each of 2 patients by the Curby cup technique.⁹ Fifty milliliters of saliva was collected by expectoration in 2 other patients whose parotid duct could not be visualized. The collection of saliva was stimulated by the use of sour lemon hard candies. The secretions were dialyzed against phosphate-buffered saline at pH 7.2 and concentrated by negative pressure dialysis. Any formed precipitate in the concentrated

*Endo Products, Inc., Richmond Hill, N. Y.

†Hyland Laboratories, Los Angeles, Calif.

secretions was removed by centrifugation at 5,000 r.p.m. for 10 minutes.

Immunoelectrophoresis of concentrated salivary or parotid secretion was performed according to the method of Scheidegger.¹⁰ A double-diffusion agar immunoprecipitation technique for detection of transport piece in salivary secretions or parotid fluid was employed with the use of antisera to transport piece obtained by immunization of rabbits with saliva from an agammaglobulinemic patient known to have no salivary IgA.¹¹ A second antitransport piece antiserum was obtained by immunizing rabbits with purified colostral IgA and absorbing with normal human serum.¹²

RESULTS

Prevalence of allergic disease

Four of the 7 patients (57 per cent) had evidence of respiratory allergy with or without flexural eczema (Table I). Two of the 4 had both extrinsic

Table I. *Clinical data and family histories in 7 patients with ACED*

<i>Patient</i>	<i>Age</i>	<i>Bronchial asthma</i>	<i>Allergic rhinitis</i>	<i>Flexural eczema</i>	<i>Food allergy</i>	<i>Family history of ACED</i>	<i>Family history of allergy</i>
K. H.	11	With upper respiratory infections and on entering barns	None	Present infancy to age 6	None	M*	M
A. S.	10	Perennial with seasonal flare Apr. to Nov.	Perennial with seasonal flare Apr. to Nov.	Present since infancy	None	M	P†
R. T.	13	Seasonal (spring, summer, fall)	Seasonal (spring, summer, fall)	Present since infancy	Asthma and angioedema with egg or peanut butter ingestion	M	M-P
J. J.	16	None	Seasonal (Aug. to Sept.)	None	None	M	M
A. P.	13	Wheezing with upper respiratory infections	None	None	None	?	None
W. R.	32	None	None	None	None	None	None
M. S.	2	None	None	Vague history of eczema at age 6 months	None	M	?

*M = maternal side of family.

†P = paternal side of family.

Table II. *Prick test reactivity to common inhalant and food allergens in 7 patients with ACED*

<i>Allergen</i>	<i>Patient</i>						
	<i>K. H.</i>	<i>A. S.</i>	<i>R. T.</i>	<i>J. J.</i>	<i>A. P.</i>	<i>W. R.</i>	<i>M. S.</i>
Stock house dust	4+	4+	Neg.	Neg.	Neg.	Neg.	Neg.
Endo house dust	Neg.	3+	4+	Neg.	Neg.	Neg.	Neg.
Elm	Neg.	4+	Neg.	Neg.	Neg.	Neg.	Neg.
Oak	Neg.	3+	Neg.	2+	Neg.	1+	Neg.
Box elder	Neg.	Neg.	Neg.	2+	3+	1+	Neg.
Orchard grass	Neg.	4+	4+	2+	Neg.	2+	Neg.
Timothy	3+	4+	Neg.	2+	Neg.	Neg.	Neg.
Dwarf ragweed	4+	4+	4+	4+	3+	3+	Neg.
Giant ragweed	4+	4+	4+	4+	3+	1+	Neg.
Alternaria	4+	3+	3+	2+	Neg.	Neg.	Neg.
Hormodendron	Neg.	Neg.	Neg.	2+	Neg.	Neg.	Neg.
Milk	4+	Neg.	3+	Neg.	Neg.	Neg.	Neg.
Wheat	Neg.	4+	1+	Neg.	Neg.	1+	Neg.
Egg	Neg.	Neg.	4+	Neg.	Neg.	Neg.	Neg.
Saline control	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

bronchial asthma and allergic rhinitis, one had extrinsic bronchial asthma without allergic rhinitis, and one had seasonal allergic rhinitis but no history of asthma. One additional patient had wheezed with upper respiratory infections but had no history suggesting extrinsic asthma. Three of the 4 patients with respiratory allergy had flexural eczema. One patient without respiratory allergy had a vague history of eczema at age 6 months, but this could not be confirmed on physical examination at age 2. The ingestion of eggs or peanut butter produced angioedema and asthma in one patient.

Family histories

Family histories were positive for ACED in 5 patients, including the 4 with allergic disease (Table I). In each case the history of ACED was confined to the maternal side of the family. Information was inadequate to determine the hereditary pattern of the disease in 2 patients, since family histories were negative and adequate numbers of relatives were not available for examination. A family history of extrinsic bronchial asthma or allergic rhinitis was present in the 4 patients with ACED and respiratory allergy. In two instances, only the maternal side of the family was involved; in one the paternal side alone; and in one both the paternal and maternal sides. Two of the 3 patients without allergic disease had negative family histories of allergy; in the third, the family history was incomplete and therefore difficult to interpret.

Prick tests reactions

Six patients (86 per cent) had positive prick test reactions to dwarf ragweed and to other common inhalant and food allergens (Table II). Four of these had clinical evidence of allergic disease, and 2 had negative allergy histories. One patient (M. S.), a 2-year-old boy, had no clear-cut history of allergy and had negative skin tests by both prick and intradermal methods.

Table III. Serum immunoglobulins, salivary IgA and transport piece, and serum P-K titers to dwarf ragweed in 7 patients with ACED

Patient	Serum immunoglobulins* (mg./100 ml.)			Salivary IgA	Salivary transport piece	Serum P-K titer to dwarf ragweed
	IgG	IgM	IgA			
K. H.	1,305	55	336	present	present	1:128
A. S.	1,100	128	220	present	present	1:256
R. T.	1,245	75	318	present†	present†	N.D.‡
J. J.	1,050	420	330	present†	present†	N.D.
A. P.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
W. R.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
M. S.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

*Normal values: IgG, 550 to 1,500 mg. per 100 ml.; IgM, 40 to 200 mg. per 100 ml.; IgA 70 to 400 mg. per 100 ml.

†Parotid fluid.

‡Not done.

Laboratory studies

Serum IgG, IgA, and IgM levels were normal in the 4 patients with ACED and allergic disease except for an elevation of IgM in Patient J. J. (Table III). The presence of IgA and transport piece was confirmed in the salivary secretions or parotid fluid of these 4 patients by immunoelectrophoresis and immunodiffusion, respectively. Passive transfer tests with dwarf ragweed revealed a reaginic antibody titer of 1:256 in Patient A. S., who had both asthma and allergic rhinitis during the ragweed season, and 1:128 in Patient K. H., who had no evidence of either ragweed hay fever or asthma.

DISCUSSION

The results suggest a high prevalence of allergic disease (extrinsic bronchial asthma, allergic rhinitis, and flexural eczema) and positive prick test reactions to common inhalant and food allergens in patients with ACED as compared to that found in the general population. This hypothesis was tested by comparing the prevalence of allergic disease and positive skin tests to common inhalant allergens found in the 7 patients with ACED with data obtained from the Tecumseh Community Health Study. Tecumseh is a community of approximately 10,000 persons located in southeastern Michigan. Since 1957, the University of Michigan has been surveying the health of the Tecumseh population.¹³ In 1962, Broder, Barlow, and Horton^{14, 15} studied the cumulative prevalence of asthma and allergic rhinitis in Tecumseh residents. Of the 6,995 persons studied by history and physical examination, 596 (8.53 per cent) had "more certain" evidence of either asthma, allergic rhinitis, or both. Another 542 persons had "less certain" evidence of one or both of these disorders. The combined "more certain" and "less certain" groups represented 1,138 individuals or 16.27 per cent of the population studied. If it is assumed that not 16.27 per cent but 20 per cent of the general population has or has had asthma, allergic rhinitis, or both, the chance of finding 4 or more persons with one or both of these diseases in a sample of 7 is < 0.04 as determined by the binomial method.

A study of prick test reactivity to common inhalant allergens in the Tecumseh population is now in progress.¹⁶ Each person examined is tested with the following materials: dwarf ragweed; a mixture of equal parts of June grass, orchard grass, redtop, and timothy; Endo house dust; a mixture of equal parts of *Alternaria* and *Hormodendron*; and a saline control. The preparation of allergenic extracts and the criteria for reading the prick tests are similar to those used in the present study of 7 patients with ACED.^{6, 7} Three hundred fifty-six of the first 2,020 unselected Tecumseh residents studied (17.6 per cent) had a 1+ or greater prick test reaction to one or more of these allergens. If it is assumed that not 17.6 per cent but 20 per cent of the general population will have a positive prick test reaction to at least one of the 4 allergenic extracts used, the chance of finding 6 positive reactors in a sample of 7 is < 0.0004 as determined by the binomial method.

The data indicate a statistically significant increase in the prevalence of allergic disease and positive prick test reactions to common inhalant allergens in patients with ACED as compared to the general population. A review of the literature suggests that others have also suspected an association between ACED and allergic disease. Although no data are given to support their contention, Butterworth and Streat² state that atopic dermatitis and asthma are the complications of congenital ectodermal dysplasia noted most frequently. In addition there are several case reports of patients with ACED who also had asthma^{1, 17} or eczema.^{1, 18}

The explanation for the increased prevalence of allergic disease in patients with ACED is not clear at present. One postulate might be that both ACED and the predisposition to develop allergic disease following exposure to allergenic substances are transmitted by a common genetic mechanism. ACED is transmitted as a sex-linked recessive, however, and there is no evidence to indicate that this is the case with allergic disease. In addition, in at least one patient (A. S.) the history of ACED was on the maternal side of the family, whereas the history of allergic disease was on the paternal side.

A more attractive hypothesis involves the observation that patients with ACED frequently have hypoplastic changes in the respiratory mucosa resulting in atrophic rhinitis, chronic pharyngitis, and laryngitis sicca. This abnormality could result in an increased permeability of the nasal mucosa, permitting inhaled allergens to penetrate the mucosal barrier and reach antibody-forming cells with stimulation of reaginic antibody production. An alternative possibility would be an abnormality in nasal secretions in patients with ACED resulting in decreased destruction of inhaled allergens with the same end result. Salvaggio and co-workers^{19, 20} have demonstrated that, whereas the immunologic responses of atopic and normal persons to parenterally administered dextran and purified crystalline bovine ribonuclease are similar with respect to development of wheal and flare skin reactivity and precipitating antibody, administration of these antigens by intranasal aerosol results in more frequent development of wheal and flare skin reactivity in the atopic group. They postulated that the nasal mucosa of atopic persons is more permeable to inhaled allergens than that of normal individuals. Data obtained in the present study provide some sup-

port for this hypothesis and suggest that ACED might be regarded as an interesting experiment of nature which will ultimately aid in our understanding of the atopic state.

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