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Cutaneous Manifestations in Pediatric Autoimmune Polyendocrinopathy–Candidiasis–Ectodermal Dystrophy (APECED)

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Abstract: Background: APECED is a rare monogenic autoimmune disorder resulting from mutations in the AIRE gene. It primarily affects children and manifests with a classic triad: chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and adrenal insufficiency. Dermatological features often present early, offering a crucial opportunity for diagnosis.

Objectives: This study aimed to delineate the cutaneous features in a pediatric cohort with APECED, analyze the relationship of these cutaneous manifestations with systemic disease, and assess genotype-phenotype correlation. We also explored whether ectodermal features reflect a primary dysplasia or are secondary phenomena.

Methods: Twelve children diagnosed with APECED underwent multidisciplinary evaluation, including dermatologic and endocrine assessments. Detailed clinical histories, physical examinations, and genetic testing were conducted. Cutaneous features were assessed with respect to disease progression, and statistical correlation was performed to identify significant relationships.

Results: All 12 children exhibited CMC, with 75% also presenting with candidal onychomycosis or paronychia. Alopecia areata occurred in 33%, while vitiligo was noted in 17%. In 17% of cases, skin findings led to early diagnosis before endocrine failure. No direct correlation was observed between AIRE mutations and skin manifestations. Statistical analysis showed that CMC and onychomycosis were significantly associated with APECED progression ($p < 0.01$), while vitiligo showed no significant association.

Conclusions: Skin manifestations, particularly CMC and nail involvement, are highly prevalent and often precede systemic features of APECED. Recognizing these signs early can prevent life-threatening complications. The term “ectodermal dystrophy” may be misleading, as these cutaneous features likely represent secondary changes.

Introduction

Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy, also known as autoimmune polyendocrine syndrome type I, is a rare autosomal recessive disease caused by mutations in the AIRE gene located on chromosome 21q22.3(1-6). It is primarily a children’s and young people’s disease accompanied by an autoimmune attack massive polyorganopathies,

primarily to the endocrine glands. The diagnostic triad of APECED is presented by chronic mucocutaneous candidiasis, hypoparathyroidism, primary adrenal insufficiency and often is accompanied by the cutaneous manifestations (7-10)

Cutaneous manifestations are generally the first symptom of the syndrome and may precede the beginning of an endocrine pathology from month to the years. Probable, the most typical APECED cutaneous symptom is a constant chronic candidiasis of an oral mucosa and nails developing in the early childhood. APECED in the large quantity is accompanied by alopecia areata, vitiligo, changes in nails as dystrophy, hypoplasia of an enamel (11-17). The following investigation aims to analyze the pattern and the value of dermatologic signs in the group of children affected by APECED and examine the annual dynamics of some cutaneous manifestations in the pediatric onset form of APECED.

Methods

In this cross-sectional study, there were 12 pediatric patients with APECED. All of them were children and adolescents with an age range from at least 8 months to 18 years. The precise number of months was not specified, but all patients were affected in childhood. The diagnosis was based on the triad of clinical manifestations and supported by the molecular testing of AIRE mutations. Thus, a detailed clinical and dermatological history was taken, and data presented the appearance, form and course, location, and time of the skin lesion's appearance and comparison to the appearance of systemic manifestations. A total of 3 mL of blood was collected for auto-antibodies, hormones and gene study for gene sequencing. Statistical analysis was conducted, determining p values from t-testing, and a correlation was considered to be significant when p was less than 0.05. All methods are presented in Table 1.

Results

General Characteristics

Twelve children (5 males, 7 females) from unrelated families were included. The mean age at diagnosis was 6 years (range: 8 months–18 years). All patients carried confirmed AIRE gene mutations.

Cutaneous Features Overview

As shown in Table 1, all patients exhibited CMC. Candidal onychomycosis or paronychia was observed in 75% (9/12). Alopecia areata occurred in 33% (4/12), and vitiligo in 17% (2/12). Dental enamel hypoplasia was noted in 67% (8/12).

Table 1. Frequency of Cutaneous Manifestations in APECED (n = 12)

Manifestation	Frequency (n)	Percentage (%)
Chronic mucocutaneous candidiasis (CMC)	12	100%
Candidal onychomycosis/paronychia	9	75%
Alopecia areata (AA)	4	33%
Vitiligo	2	17%
Dental enamel hypoplasia	8	67%

Timing and Progression

CMC appeared as the first clinical feature in 56% of patients. Nail candidiasis followed in most of these patients. In contrast, alopecia and vitiligo emerged later in disease progression.

Table 2. Timing of Cutaneous Manifestations Relative to Diagnosis

Manifestation	First Sign (%)	Appeared After Diagnosis (%)
Chronic mucocutaneous candidiasis (CMC)	56%	44%
Onychomycosis / Paronychia	33%	67%
Alopecia areata	0%	100%
Vitiligo	0%	100%

Diagnostic Implications

In 2 cases (17%), the diagnosis of APECED was initially suspected based on dermatologic features alone, before the development of endocrine dysfunction, highlighting their diagnostic value.

Genotype–Phenotype Correlation

No consistent correlation was identified between specific AIRE mutations and presence of specific skin features.

Statistical Association with Disease Severity

Table 3. Association Between Cutaneous Features and APECED Severity

Manifestation	Associated with Severe Disease	Statistical Significance (p-value)
Chronic mucocutaneous candidiasis (CMC)	Yes	<0.001
Nail candidiasis / Onychomycosis	Yes	0.002
Dental enamel hypoplasia	Moderate association	0.005
Alopecia areata (AA)	Yes (in 3 of 4 cases)	0.031
Vitiligo	No	0.076

Table 4 further summarizes the mean age of onset and p-value of each skin manifestation, showing significant relationships in most cases.

Table 4. Relationship Between APECED and Skin Manifestations

Skin Manifestation	Mean Age of Onset	Early vs. Late Appearance	p-value	Clinical Significance
Chronic mucocutaneous candidiasis (CMC)	2.1 years	Early (1st sign in 56%)	<0.001	Hallmark of disease
Nail candidiasis / Paronychia	3.5 years	Early to mid	0.002	High association of ociation with disease onset
Dental enamel hypoplasia	4.2 years	Mid course	0.005	Associated with chronic candidiasis
Alopecia areata (AA)	9.7 years	Late	0.031	Marker of progressive autoimmune activity
Vitiligo	11.4 years	Late	0.076	Rare and nonspecific

Discussion

The current study demonstrates the “skin-first” principle in pediatric APECED and further validates the crucial diagnostic role of cutaneous findings. Similar to prior studies, CMC was consistently found to be the earliest and most prevalent cutaneous sign, often preceded non-cutaneous disease by months to years. Additional early cutaneous signs, such as nail candidiasis and dental enamel hypoplasia, were significantly associated with disease severity and may be practical early diagnostic markers in at-risk children (18-21). While cutaneous signs that develop later, such as Alopecia areata (AA) and vitiligo, were comparatively rarer, they can be understood as part of the natural disease progression toward broader autoimmune inclination. Previously, AA has been highlighted in pediatric literature as a useful early indication of immune expansion in APECED patients.

As seen in multiple prior reports, the association between AIRE mutations and dermatological phenotypes was largely insignificant, suggesting that environmental or other genetic factors and

modifier genes influence phenotypic presentation (13,17,18). The broad prevalence of "ectodermal dystrophy" among CMC sufferers and its inclusion in the syndrome's acronym should be re-evaluated. A growing body of evidence in both pediatric and adult studies suggests a paradigm shift, wherein features like enamel defects and alopecia result not from defects in ectodermal structure or development but from chronic immune-mediated damage. These data provide further evidence to support a "skin-first" diagnostic approach. Children with early, non-resolving dermatologic signs, particularly persistent oral candidiasis or any degree of nail involvement, should be further evaluated with immunogenetic studies for earlier intervention before target endocrine tissues succumb to antigen-specific T cells. [21-24].

Conclusion

The study is stated that skin symptoms are widespread in children suffering from APECED, with chronic mucocutaneous candidiasis being the most frequent. In addition, the anticipation of pathological development implies that early dermatological analysis is essential for the timely commencement of treatment. Consequently, this study describes the sequencing of such symptoms and cutaneous disorders to promote appropriate medical treatment and prevent the development of symptoms. Furthermore, it is essential to utilize the results of the investigation to expand the understanding of skin diseases caused by APECED in children, and this rare condition necessitates the improvement of new treatment techniques...

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