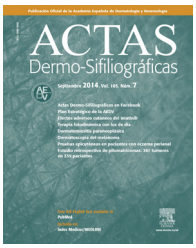
Actas Dermosifiliogr. 2016;107(2):116–124

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



PRACTICAL DERMATOLOGY

# Differential Diagnosis of Genetic Disorders Associated with Moderate to Severe Refractory Eczema and Elevated Immunoglobulin E☆

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Received 29 June 2015; accepted 19 September 2015
Available online 1 February 2016

**KEYWORDS**
Immunoglobulin E;
Atopic dermatitis;
Atopic eczema;
Genetic diseases;
Differential diagnosis;
Immunodeficiency

**Abstract** The association of moderate to severe eczema and elevated plasma levels of immunoglobulin E is a characteristic not only of atopic dermatitis but also of various genodermatoses: hyperimmunoglobulin E syndromes, Omenn syndrome, Netherton syndrome, peeling skin syndrome type B, severe dermatitis, multiple allergies, and metabolic wasting syndrome, Wiskott-Aldrich syndrome, prolidase deficiency, Loeys-Dietz syndrome, IPEX syndrome, STAT5B deficiency, and pentasomy X. The clinical presentation of these genodermatoses –typically in children– is consistent with severe atopic dermatitis. Immunoglobulin E is elevated from birth and response to conventional treatments is poor. Diagnosis is further complicated by the fact that these genodermatoses often share other clinical manifestations and laboratory findings. We present practical guidelines for differentiating among these various entities, with the aim of helping physicians decide what type of genetic test should be carried out –and when– in order to establish a definitive diagnosis.


**PALABRAS CLAVE**
Inmunoglobulina E;
Dermatitis atópica;
Eccema atópico;

## Trastornos genéticos con eccema moderado-grave refractario y elevación de inmunoglobulina E: diagnóstico diferencial

**Resumen** La asociación de eccema moderado-grave y niveles elevados de IgE en plasma es característica no solo de la dermatitis atópica, sino también de diversas genodermatosis:

☆ Please cite this article as: Arjona Aguilera C, Albarrán Planelles C, Tercedor Sánchez J. Trastornos genéticos con eccema moderado-grave refractario y elevación de inmunoglobulina E: diagnóstico diferencial. Actas Dermosifiliogr. 2016;107:116–124.

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Enfermedades genéticas;
Diagnóstico diferencial;
Inmunodeficiencia

síndromes hiper-IgE, síndrome de Omenn, síndrome de Netherton, síndrome de la piel exfoliada tipo B, síndrome de dermatitis grave-alergias múltiples-desgaste metabólico, síndrome de Wiskott-Aldrich, déficit de prolidasa, síndrome de Loeys-Dietz, síndrome IPEX, déficit de STAT5B y pentasomía X. Se trata de pacientes pediátricos que presentan un cuadro clínico compatible con dermatitis atópica grave, con mala respuesta a los tratamientos clásicos y que asocian elevación de IgE desde el nacimiento. Además, comparten con frecuencia otras manifestaciones clínicas y analíticas, lo cual dificulta el diagnóstico. Presentamos una guía práctica para orientar el diagnóstico diferencial entre todas estas entidades y, por lo tanto, ayudar a decidir cuándo y el tipo de test genético a realizar para establecer el diagnóstico definitivo.


The association between moderate-to-severe eczema and elevated plasma immunoglobulin (Ig) E levels is characteristic of atopic dermatitis and is also seen in other genetic diseases. Many patients also have concurrent congenital immunodeficiency. When faced with a patient with clinical signs and symptoms consistent with severe atopic dermatitis[1] who does not respond to traditional treatments (hygiene and dietary interventions, topical or systemic corticosteroids, cyclosporin, methotrexate, or azathioprine)[1] and has elevated IgE from the first days of life, we should suspect the presence of one of these syndromes.

One group, hyper-IgE syndromes, has been described and extensively studied. These entities are classified according to the pattern of transmission: autosomal dominant (AD) or autosomal recessive (AR). Both types are characterized by elevated IgE and a clinical picture dominated by skin involvement, with moderate or severe acute and subacute eczema that resembles atopic dermatitis, and by recurrent skin and respiratory infection.

The other group comprises a series of low-prevalence congenital diseases that often present with episodes of refractory eczema associated with elevated IgE and that should be included in our diagnostic algorithm. Omenn syndrome is a serious combined immunodeficiency of AR transmission that presents in the first year of life. Wiskott-Aldrich syndrome is a primary X-linked immunodeficiency characterized essentially by bleeding diathesis secondary to thrombocytopenia or platelet dysfunction, along with recurrent eczemas and bacterial infections from birth. Prolidase deficiency is a multisystemic disease of AR transmission with a very variable clinical presentation and severity, associated with limited or no prolidase enzyme in erythrocytes, leukocytes, or fibroblasts. Loeys-Dietz syndrome is a connective tissue disease of AD transmission that is associated with a marfanoid appearance and abnormalities in the great arteries. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a serious congenital autoimmune disease in which refractory diarrhea, infections, and multiple endocrine disorders are present in addition to skin involvement. STAT5B deficiency is a condition of AR transmission included in the group of syndromes related to growth hormone insensitivity. This entity is notable for the occurrence of primary immunodeficiency. Pentasomy X is a congenital disease caused by chromosomal abnormalities in women leading to gonadal dysfunction, delayed development, short stature, and musculoskeletal and craniofacial malformations. Netherton syndrome is an AR genodermatosis characterized by ichthyosiform erythroderma, trichorrhexis invaginata, and atopic manifestations present almost from birth. Finally, we include 2 very recently described genodermatosis related to Netherton syndrome from the pathophysiological point of view: peeling skin syndrome type B (PSS-B) and severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome. PSS-B is an AR genodermatosis with ichthyosiform erythroderma from birth which, in addition, presents with severe food allergies, angioedema, and urticaria. Finally, SAM is another rare AR genodermatosis in which skin involvement is combined with notable food allergies, esophageal involvement, and other characteristics that will be discussed later in this article.

Differential diagnosis of these syndromes can be very complex, given that there may be considerable overlap and many clinical characteristics are shared. The phenotypic expression of each of these conditions may also vary from one individual to another. Thus, in this article, we provide key information to enable differential diagnosis from the clinical point of view, with the intention of guiding which genetic studies to request. Definitive diagnosis is made by identifying the causal mutation. In Table 1, we have compiled the main genodermatosis that should be included in the differential diagnosis, indicating the main characteristics to investigate in the diagnostic procedure to enable us reach a full diagnosis. A complete detailed description of each of these diseases is not an objective of this article. For this, the reader is referred to literature for more information.

It should be noted from the outset that the skin manifestations have a very early onset and many of these are common to several entities. Dermatitis (erythema, intense pruritus, dry skin, and lichenification) is moderate or severe in both types of hyper-IgE syndromes,[2–5] Wiskott-Aldrich syndrome,[6,7] Netherton syndrome,[6,8] SAM,[6] IPEX syndrome,[3,9] and STAT5 deficiency,[9,10] but is less frequent in PSS-B,[6] Loeys-Dietz syndrome,[11] and prolidase deficiency.[12] Generally, these conditions follow a severe course with poor response to the traditional topical and systemic treatments used in atopic dermatitis. However, seborrheic dermatitis-like lesions are much more common in Omenn syndrome. In all entities, erythroderma may present with variable frequency, and even in Netherton syndrome and PSS-B, ichthyosiform erythroderma will be a dominant feature of the clinical picture and will present at a very early