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Article Type: Supplement Article

Short Title: Clinical heterogeneity and differential diagnosis of AD, M. Deleuran and C. Vestergaard

Clinical heterogeneity and differential diagnosis of atopic dermatitis

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Funding sources

This work was supported by an unrestricted grant from Pierre Fabre Dermo-Cosmétique, France.

Conflicts of interest

M.D. is an investigator for AbbVie A/S, MSD and Pierre Fabre Dermo-Cosmétique. She is also on advisory boards for Meda Pharma, Leo Pharma, Merck Research Laboratories and Astellas, and a speaker for Leo Pharma and Pierre Fabre Dermo-Cosmétique. C.V. is an investigator for AbbVie A/S, Pierre Fabre Dermo-Cosmetique. He has served on advisory boards for Astellas Pharma and has been a speaker for Leo-Pharma, Astellas, MSD, AbbVie and Pfizer.

Summary

Atopic dermatitis (AD) is a chronic or chronically relapsing skin disease that usually presents for the first time before the age of 20 years. The disease displays great clinical heterogeneity and may resemble a number of different disorders, making the correct diagnosis of AD a significant challenge for physicians. Based on the Hanifin and Rajka criteria, the authors outline the common symptoms of AD and provide an overview of the differential diagnoses to help distinguish AD from other conditions within the clinic.

Atopic dermatitis (AD) is a chronic or chronically relapsing skin disorder related to other atopic diseases, including allergic rhinoconjunctivitis, asthma, urticaria and food allergy. It is most prevalent in infants, children and young adults, but can occur in all age groups. Only around 2% have their debut of the disease after the age of 20 years.

There is great clinical variation in the objective findings of AD (Fig. 1), but the most consistent symptom for patients with AD is atopic itch, which can have a significant impact on their quality of life. AD is a clinical diagnosis based on the presence of visible eczema with a characteristic history of the disease. There are no diagnostic tests that can confirm the diagnosis.

Clinical findings in atopic dermatitis

The best summary of symptoms and objective signs of the disease can be found in the criteria described by Jon Hanifin and Georg Rajka in 1980 (Table 1).¹ The distribution of the eczema is dependent on the patient's age but can be found on most of the skin in severe cases. In the acute phase of AD, the skin is erythematous with papules and vesicles and often secondarily infected with *Staphylococcus aureus*. In the chronic phase, the skin is infiltrated, dry and often lichenified with scales and fissures. In severe cases the disease can develop into erythroderma.

Age of onset

The eczema in AD is not present at birth, but often develops during the first weeks of life with approximately 90% of cases starting before the age of 4 years.² In infants suffering from AD, the scalp, cheeks and extensor side of the extremities are the most commonly involved areas. Flexural areas may also be involved, especially the neck fold. The midline of the face and the tip of the nose, in particular, are always spared (Yamamoto's sign).

Between the age of 1 and 4 years, the most common sites for the eczema associated with AD are the flexural areas of the skin, especially the cubital and knee folds, the wrists and ankles, and the face and hands. Dry skin and fissuring behind the ears or on the earlobe are also characteristic signs of the disease.

In older children, teenagers and adults, the flexural areas are still affected and eczema is often present on the hands and feet. Head and neck dermatitis are part of the disease spectrum in

teenagers and adults, and can be a sign of sensitization to the yeast *Malassezia furfur*. This microorganism is part of the normal flora of the skin and is, therefore, impossible to eradicate.

Minor criteria

The Hanifin and Rajka minor criteria describe many of the characteristics of the disease, including the association between AD and ichthyosis. For many years, attention focused mainly on the inflammatory processes occurring in the skin in AD, until a paper by Colin Palmer and colleagues,³ published in 2006, changed this concept. They identified two independent loss-of-function genetic variants in the gene encoding the skin barrier protein filaggrin as very strong predisposing factors for AD. They also showed that impaired skin barrier function is fundamental in the development of both AD and asthma.³ Furthermore, it has been shown that children suffering from both a filaggrin mutation and AD have a more severe form of the disease with more widespread eczema, especially on the cheeks and dorsal aspect of the hands.⁴ Dry skin is a hallmark for AD, and some patients suffer from concomitant ichthyosis. The percentage of patients with AD and dry skin differs between studies but is reported to be between 48% and 100%, compared with 14–40% in controls.^{5,6}

Several groups have investigated the prevalence of the minor criteria described by Hanifin and Rajka. Böhme *et al.*⁵ found seven of the criteria were seen more often in small children with AD, examined at the age of 2 and 4 years, compared with healthy controls. These were xerosis of the skin; skin reactions provoked by food consumption; itch when sweating; hand eczema; positive skin prick test; facial erythema; and symptoms influenced by environmental factors.⁵

A recent study from the U.S.A. has provided evidence for the climate-influenced prevalence on eczema. Combined high ultraviolet radiation exposure and temperature appear to have protective effects specific to eczema; whereas a combination of high humidity and precipitation is associated with increased eczema.⁷

Other signs of AD, not included in the Hanifin and Rajka criteria, are atopic winter feet, earlobe rhagades, retro-auricular fissuring, and chronic eczema in the genital area in adults.¹

Special variants of atopic dermatitis

Sharply demarcated patches and plaques of inflamed skin are characteristic of nummular or discoid eczema, and are very often secondarily infected with *S. aureus*. The extremities and buttocks are the most commonly affected areas, and this variant is often very difficult to treat.

Patchy pityriasiform lichenoid eczema (the follicular type of AD) is common in Japanese patients. This variant is characterized by plaque-shaped, lichenoid, scaly eczema and skin-coloured follicular papules, mainly on the lateral aspects of the trunk.⁸

Another variant of AD is juvenile papular dermatosis, first described by Sutton in 1956.⁸ It is localized mainly to the elbows and knees and is thought to be associated with pollinosis as it primarily occurs in the spring and summer.

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Patients of colour and other patients with dark skin often suffer from a papulonodular form of AD with post-inflammatory hyperpigmentation.

Differential diagnosis of atopic dermatitis

Although the diagnosis of AD is often very clear, there may be cases when other diseases look like AD and vice versa. Differential diagnoses are dependent on the age of the patient and may differ between infants and adults. They can be divided into inflammatory skin diseases, infectious diseases, malignant diseases, congenital disorders, immune deficiencies, metabolic disorders and certain reactions to drugs.

Inflammatory skin diseases

Seborrhoeic dermatitis is the most common differential diagnosis in infants, and it may be virtually impossible to distinguish from AD. The clinical characteristics of seborrhoeic dermatitis in the infant are early onset; greasy rather than dry scaling skin; salmon red skin; the involvement of the scalp (cradle cap); and often the absence of pruritus. The histology of seborrhoeic dermatitis does not offer any help in distinguishing between the two diseases. However, in the adult the clinical presentation of seborrhoeic dermatitis along with greasy skin and scales on the eyebrows, nasolabial folds and retro-auricular area, as well as scalp dandruff, differentiates this disease from AD.⁹

Contact dermatitis may also be seen in infants and can be very difficult to distinguish clinically from AD, although a very specific localization and history of locally applied irritants eliciting eczema can indicate contact dermatitis. The most common allergens in children are nickel sulphate, ammonium persulfate, gold sodium thiosulfate, thimerosal and toluene-2,5-diamine.¹⁰ In adults, contact dermatitis may also look like AD but is often restricted to the areas of the skin that are exposed to the allergen.

Gianotti–Crosti syndrome (infantile papular acrodermatitis) is a disease affecting children between 2 months and 2 years of age. It is characterized by papulovesicular lesions on the face and distal parts of all four limbs and may be easily mistaken for AD.¹¹

Zinc deficiency (acrodermatitis enteropathica) may also resemble AD but the lesions are usually located periorally. The condition usually affects bottle-fed children a few days to weeks after birth.¹² Premature children have a higher risk of developing zinc deficiency.

Infections in the skin

Infestation with *Sarcoptes scabiei* gives the skin an intense pruritus, which, along with the erythematous papular lesions, may lead to a mistaken diagnosis of AD. However, the lesions caused by this infection are often found on the soles of the feet in infants and in the genital area of adults. Diagnosis can be made by the isolation of a mite typically found in burrows located between the fingers, on the wrist and in the genital area.¹³ Patients with AD develop scabies infections more easily and more severely than other individuals, due to the defect in their skin barrier function.

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Impetigo (the infection of the skin with *S. aureus*), as well as candidiasis and herpes simplex infections may be confused with AD, but can also be complications of AD.¹⁴

Patients recently infected with the human immunodeficiency virus (HIV) may develop an eczematous condition that resembles AD. In adult patients with no history of AD and a sudden onset of generalized eczema and lymphadenopathia, a diagnosis of HIV should be considered.¹⁵

Immunological diseases

Dermatitis herpetiformis (DH), a skin manifestation closely linked to gluten-sensitive enteropathy in which IgA is deposited in a granular pattern along the dermal-epidermal border, may resemble AD. However, all patients with DH have positive antigliadin antibodies and their condition improves on changing to a gluten-free diet.¹⁶

Pemphigus foliaceus (PF) is a bullous disease in which the blisters are located very superficially in the epidermis due to IgG antibody deposits in the upper third of the epidermis. Because the blisters are located very superficially, the denudated areas may appear as eczematous lesions resembling AD. In both DH and PF, immunohistochemical staining of skin biopsies provides conclusive diagnoses.¹⁷

Malignant diseases

Patients with cutaneous T-cell lymphomas (mycosis fungoides, MF) may have an eczematous appearance in the early stages, which is often misdiagnosed as AD. However, a biopsy will reveal the characteristic pleomorphic nuclei of the cell infiltrate and other diagnostic features of this lymphoma, such as Pautrier microabscesses. Clonality of the infiltrating T cell, determined by T-cell receptor clonality analysis, may also indicate cutaneous T-cell lymphoma. In the erythrodermic stage (Sézary syndrome), MF also resembles acute generalized AD.¹⁸

Histiocytosis X (Letterer-Siwe disease) is primarily a paediatric disease. Langerhans cell histiocytosis may be unifocal (skeletal) or multifocal (skeletal and visceral) and lesions in the skin of the scalp, head and neck may mimic AD and seborrhoeic dermatitis. The severity of histiocytosis ranges from a mild cutaneous disease to a life-threatening systemic disease.¹⁹

Congenital diseases

Ichthyosis vulgaris (IV) is a disease caused by mutations in the *FLG* gene, which codes for the protein filaggrin. Patients with IV are homozygotes for stop mutations in the *FLG* gene and have generalized eczematous lesions and dry skin resembling AD very closely. One may question whether the eczematous lesions of IV actually are AD, as a third of all patients with AD are heterozygotes for stop mutations in the *FLG* gene and the presence of stop mutations in the *FLG* gene increases the risk of AD by a factor of 13.³

Netherton syndrome (NS) is caused by stop mutations in the *SPINK5* gene, which codes for LEKTI, a protease inhibitor. Under normal circumstances, LEKTI inhibits the proteases that break down structural proteins in the epidermis, such as the corneodesmosomes and,

perhaps, filaggrin. Clinically, patients with NS have a very specific dermatitis, named ichthyosis linearis circumflexa, in which eczematous lesions spread over the skin in a serpiginous linear pattern with double-edged scales. Furthermore, they have bamboo hair (trichorrhexis invaginata), increased IgE and eosinophilia and parents of the child often report that the child is unable to grow long hair.²⁰

Hyper IgE syndromes

Hyper IgE syndromes (HIES) are rare primary immunodeficiencies associated with severe eczema, recurrent *S. aureus* abscesses and pneumonias, and very high serum IgE levels. They are inherited in an autosomal dominant manner through mutations in the signal transducer and activator of transcription 3 (STAT3) (AD-HIES)²¹ or in an autosomal recessive manner (AR-HIES) through mutations in the dedicator of cytokinesis 8 protein (DOCK8).²² Patients with AD-HIES present with abscesses of internal organs, severe infections, pneumatoceles, nail and mucocutaneous candidiasis, bone fractures, scoliosis, and a positive family history of HIES. Patients with AR-HIES, on the other hand, present with infections typical for cellular immunodeficiencies, cutaneous viral infections and recurrent sinopulmonary disease.

Conclusion

In conclusion, AD is a fascinating disease with many different clinical presentations that will vary according to the age of the patient and whether the patient suffers from any associated disorders. AD is a clinical diagnosis but if a differential diagnosis is considered, a skin biopsy should be performed.

Acknowledgments

The authors would like to thank MedSense Ltd, High Wycombe, U.K., for providing editorial assistance which was funded by Pierre Fabre Dermo-Cosmétique, France.

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Figure legends

Fig 1. Clinical presentations of atopic dermatitis (AD). (a) Diffuse severe childhood AD and prurigo. (b) Head and neck dermatitis in a young adult. (c) Fissure on the earlobe. (d) Eczema with severe impetigo. (e) Eczema herpeticum. (f) Pityriasis alba. (g) Nummular type of AD. (h) AD complicated by allergic contact dermatitis. (i) Dennie–Morgan fold. (j) Atopic winter feet. The authors would like to acknowledge Professor Niels Veien from Aalborg, Denmark for providing the clinical picture (b) from his online clinical database, Danderm.

Table 1. Hanifin and Rajka’s criteria for atopic dermatitis (AD)¹

Three or more basic features required • Pruritus • Typical morphology and distribution: ○ Flexural lichenification or linearity in adults ○ Facial and extensor involvement in infants and children • Chronic or chronically relapsing dermatitis • Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Plus three or more minor features • Xerosis • Ichthyosis/palmar hyperlinearity/keratosis pilaris • Immediate (type I) skin test reactivity • Elevated serum IgE • Early age of onset • Tendency towards cutaneous infections (esp. <i>Staphylococcus aureus</i> and herpes simplex)/impaired cell-mediated immunity

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- Tendency towards nonspecific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie–Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/emotional factors
- White dermographism/delayed blanch

