



Red face revisited: Endogenous dermatitis in the form of atopic dermatitis and seborrheic dermatitis

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Abstract Atopic dermatitis and seborrheic dermatitis are multifactorial dermatitides that are known collectively as *endogenous dermatitis*. Both conditions can affect the face, but they have clinical, epidemiological, and physiopathological peculiarities that distinguish them from each other. These two diseases are very common all around the world. Atopic dermatitis is associated with xerosis and increased susceptibility to irritants and proteins; patients with this condition have a tendency to develop asthma, allergic rhinitis, and systemic manifestations that are mediated by immunoglobulin E. Seborrheic dermatitis is a moderate chronic dermatitis that is restricted to regions with a high production of sebum and areas that have cutaneous folds. There are many studies about pathophysiology related to the immunology and genetics of atopic dermatitis, but little is known about the genetic and immunological markers of seborrheic dermatitis.

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Introduction

Atopic dermatitis (AD) and seborrheic dermatitis (SD) are multifactorial dermatitides that are known collectively as *endogenous dermatitis*. They have different clinical, epidemiological, and pathophysiological characteristics.

AD is common around the world and can occur among individuals of any age, although in the vast majority of patients it begins before the age of 5 years. There are three stages of life at which AD is most likely to occur: infancy, puberty, and adulthood. AD is associated with xerosis and increased susceptibility to irritants and proteins. Patients with AD have a tendency to develop asthma, allergic rhinitis, and systemic manifestations that are mediated by immunoglobulin E.

SD is a moderate chronic dermatitis that is restricted to regions with a high production of sebum and areas that have cutaneous folds. The link between the overproduction of sebaceous secretions and *Malassezia sp* has been accepted as obvious.

Studies of the pathophysiology of both AD and SD also strive to uncover information about the immunology and genetics of these conditions. For AD, these studies are advancing, whereas little is known about genetic and immunological markers of SD.

In this contribution, we shall review these two diseases that can affect the face; we shall especially focus on pathophysiology and new findings in that area, which are the most controversial aspects of these diseases. AD was the first disease that involved the discussion of whether the primary triggering event was immunological (“inside to outside”) or environmental (“outside to inside”); we extrapolated these inside-outside and outside-inside theories for SD.

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Atopic dermatitis

AD is a chronic inflammatory disease that is usually accompanied by other cutaneous atopic manifestations (ie, the “atopic march”), such as xerosis, keratosis pilaris, and palmar and plantar hyperlinearity (Figures 1 through 4).¹ It often precedes or occurs with food allergies, asthma, or rhinitis.² AD has two phases of onset: early onset (during childhood, particularly the first 2 years of life) and late onset (after puberty).

Acute AD lesions are erythematous, oozing papules or plaques with variable degrees of pruritus (ie, acute dermatitis). There may be excoriations as a result of scratching. If the lesion develops a secondary infection, which will often be staphylococcal, then the lesion will become more exudative and have serous crusting. A chronic lesion is often affected by prolonged scratching and thus has a thicker, hyperkeratotic, and lichenified plaque, sometimes with ulcerations and prurigo nodularis (Figure 5).¹

Epidemiological studies currently suggest that increasing urbanization and social-class gradients are related to the triggering of dermatitis; there is a stronger association of these conditions in developing countries and among individuals with a higher socioeconomic level.³

External agents

Pruritus is the cardinal feature of AD, and it is characterized by a cutaneous sensation that provokes scratching of the skin. Severe pruritus negatively affects the quality of life of the affected patients.⁴

Antimicrobial peptides (AMPs) such as cathelicidins and defensins have been found to be deficient in the skin of patients with AD,⁵ so the antimicrobial barrier in these



Fig. 2 Atopic dermatitis on the face.

individuals is compromised. AMPs play a particularly important role in innate immunity. AMPs are evolutionarily well-conserved short (less than 100 amino acids) gene-encoded proteins; they have a broad antimicrobial spectrum and are able to kill gram-positive and gram-negative bacteria, viruses, and fungi. Keratinocytes and other resident cells in the skin (eg, eccrine gland cells, mast cells, sebocytes) produce and secrete AMPs.⁶

The impaired expression of AMPs causes bacterial colonization that can promote or trigger antibody production



Fig. 1 Atopic dermatitis on the face.



Fig. 3 Pityriasis alba.

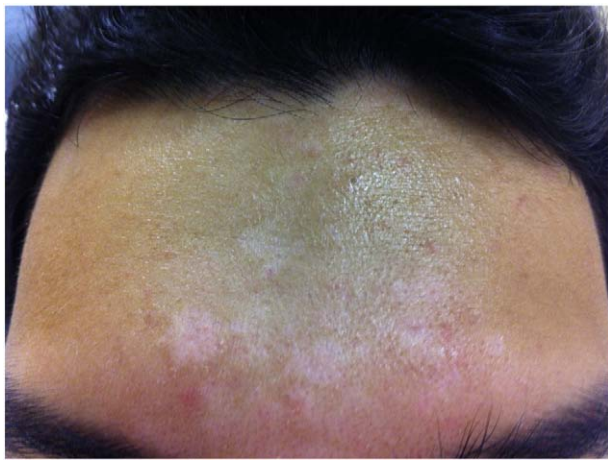


Fig. 4 Atopic dermatitis on the forehead.

via antigens or superantigens and thus induce immunoglobulin-E-specific responses,⁷ which in turn induce the development of AD.⁸ Almost 90% of patients with AD are colonized with *Staphylococcus aureus*.

Evidence suggests that the reduced expression of AMP is not a result of a primary defect of the epidermis but rather a result of the inhibitory effects of the TH2 cytokines (interleukins 4 and 13) and the immunomodulatory cytokine (interleukin 10) on keratinocytes.⁹ For example, the use of topical corticosteroids, which are one of the major therapeutic agents, can reduce the expression of AMP and increase the tendency of *S aureus* colonization in the skin of patients with AD.

Other irritant agents or allergens can promote or initiate the inflammatory process via their penetration of a dysfunctional epidermal barrier.

Genetics

There are many new considerations in the field of genetics that apply to AD. It is believed that the filaggrin (FLG) gene mutations are the main predisposing factor for AD. The designation *filaggrin* is derived from “filament-aggregating protein”; the FLG gene encodes a

protein with the same name that promotes the aggregation of keratin intermediate filaments to form a highly insoluble keratin matrix. This matrix acts as a protein scaffold for the attachment of cornified cell-envelope proteins and lipids that together form the stratum corneum, which is an external component of the epidermal barrier.¹⁰

Despite some evidence against this theory,^{11–13} when the FLG gene is mutated, the result is an FLG deficiency and the decreased production of polycarboxylic acids such as pyrrolidine carboxylic acid and transurocanic acid. Its direct consequence is an increase in the pH of the stratum corneum. This increase in pH leads to the activation of multiple serine proteases that cause the generation of interleukins 1 α and 1 β ; this is considered the first step in the cytokine cascade that leads to inflammation in patients with AD.⁷

Although 14% to 56% of European patients with AD do not have any of the known FLG mutations and approximately 40% of patients with FLG-null alleles never develop AD,^{13,14} some authors have described a correlation between the severity of the disease and FLG mutations with barrier impairment¹⁵ as demonstrated by an increase in transepidermal water loss detected in subjects with homozygous FLG variants.¹⁶ Another study did not demonstrate the same findings that occur in patients with ichthyosis vulgaris, who have FLG mutations but no inflammation.¹⁶

The dysfunctional epidermal barrier is an important factor in the physiopathogenesis of atopic dermatitis.¹⁷ The normal processes of the proliferation and differentiation of keratinocytes depend on the maintenance of the epidermal calcium gradient, which is inversely proportional to transepidermal water loss.¹⁸

The human-tissue kallikreins belong to the serine protease family. These substances degrade the corneodesmosomes that maintain adhesion between keratinocytes and that process lipid precursors; these precursors are secreted by lamellar bodies and released into the stratum granulosum/stratum corneum interface and into ceramides and free fatty acids.⁷

Another mechanism related to the increase is serine protease function is the signaling of the plasminogen activator type 2 receptor and lamellar body secretion downregulation, which causes the failure of lamellar body secretion and which consequently results in a decrease in stratum corneum lipids in patients with AD.⁸

The proof of the effects of excess serine protease activity in the pathogenesis of AD arises from an autosomal-recessive disorder caused by mutations in SPINK5, which is the gene that encodes the serine protease inhibitor that causes Netherton syndrome.⁸

Other genes were seen in recent large-scale, genome-wide association studies of 11,025 patients with AD and 40,398 control individuals.¹⁹ A novel susceptibility locus was identified on 11q13.5 downstream from C11orf306, and a



Fig. 5 Prurigo nodularis.

ATOPIC DERMATITIS

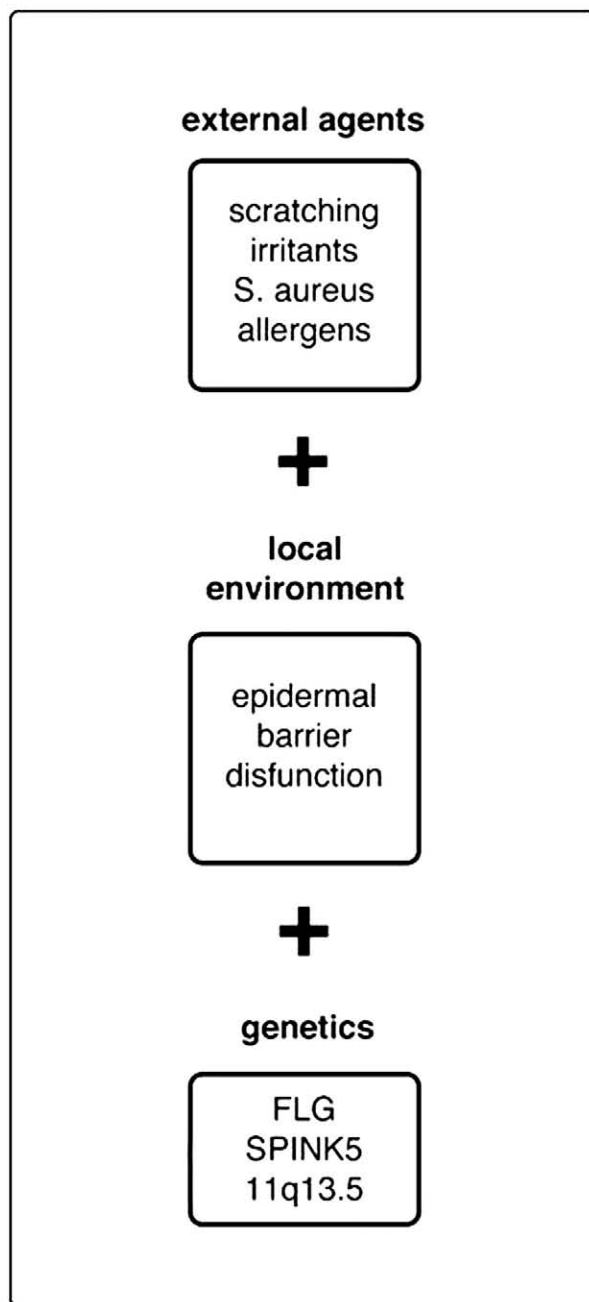


Fig. 6 Predisposing factors for atopic dermatitis.

genome-wide significant association signal from within the cytokine cluster on 5q31 was also observed. These genes are associated with the expression of interleukin 13. The same study identified other signals in the FLG locus (ie, the epidermal differentiation complex).¹⁹

A second recent genome-wide association study looked at a Han Chinese population and identified two novel loci, rs6010620 and 20q13.33, one of which also demonstrated evidence of association in a German sample.²⁰

It is currently believed that, with AD, there is some involvement of a genetic component (ie, FLG, SPINK5, and other genes) that can induce a reduction in the skin barrier (ie, defective permeability and antibiotic functions) and also trigger inflammation by leading to the expression of cytokines (eg, interleukin 1). The reduction of the epidermal barrier would predispose individuals with AD to the colonization of *S. aureus* on the skin. The *S. aureus* superantigens would then influence the inflammatory process, which is revealed by itching, and contact with irritating substances and allergens in the environment may also cause inflammation and pruritus (Figure 6).

Pruritus leads patients to vigorously scratch the skin, and this causes the typical cutaneous lesions and excoriated, ulcerated, and lichenified plaques of dermatitis. This is the “inside-outside” theory that describes AD as an immunological and inflammatory disease that is triggered by an immunological abnormality. Other authors support the “outside-inside” theory by stating that the initial event is environmental; they justify their point of view by saying that the restoration of the lipid abnormality in the epidermal barrier can downregulate the “inside-outside” alterations.²¹ We propose that there is participation from both internal and external factors in a patient who develops AD.

Seborrheic dermatitis

SD is a chronic inflammatory disease that affects approximately 3% to 5% of young adults; men are more often affected than women, and the condition is more common among HIV-positive individuals.²² SD has two incidence peaks: the newborn period (after the age of 3 months) and adulthood (between approximately 30 and 60 years of age).²³ The bimodal presentation of this disease suggests the involvement of sex hormones in its pathogenesis.

SD has distinct characteristics that depend on the patient’s age. The pediatric form is self-limited and probably related to the reduction of maternal serum levels of circulating hormones; this form is the most similar to AD. In adults, the disease tends to be chronic, with frequent periods of recurrence.²⁴

SD lesions are erythematous and scaly. They display marked variations in size and several degrees of intensity. The plaques are located predominantly on the scalp, the face, the upper trunk, and the flexures, which are all sites of greater sebaceous production (Figures 7, 8, and 9).

Patients with HIV show the same clinical lesions, but they are more extensive, more intense, and more refractory to treatment. SD usually affects patients with CD4+ T-lymphocyte counts of between 200 and 500/mm³ and thus is considered an early marker of AIDS.²⁵

In children, SD occurs most frequently during the first 3 months of life. Scaling of the scalp, which is also called

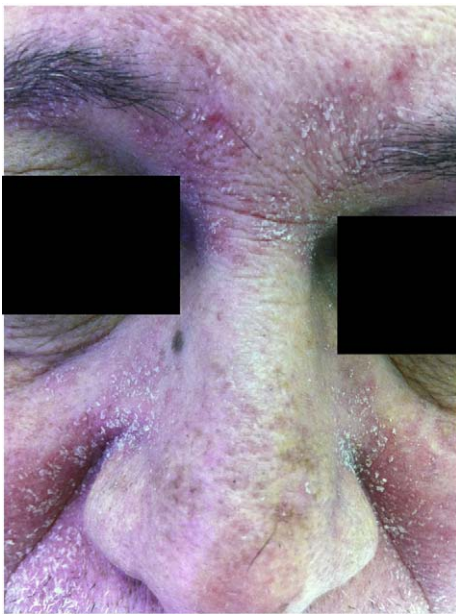


Fig. 7 Seborrheic dermatitis on the face.

cradle cap, is the most common clinical presentation and seen in 42% of affected patients.²⁶ The condition is characterized by the appearance of yellowish adherent scales soon after birth. It can also occur on the face and in the folds of the skin (ie, retroauricular area, neck, axilla, groin).²⁶

The differential diagnoses for SD include psoriasis, atopic dermatitis, tinea capitis, cutaneous lymphoma, and Langerhans cell histiocytosis.²⁶ The childhood form of SD is similar to the childhood form of AD, but the affected sites (ie, the

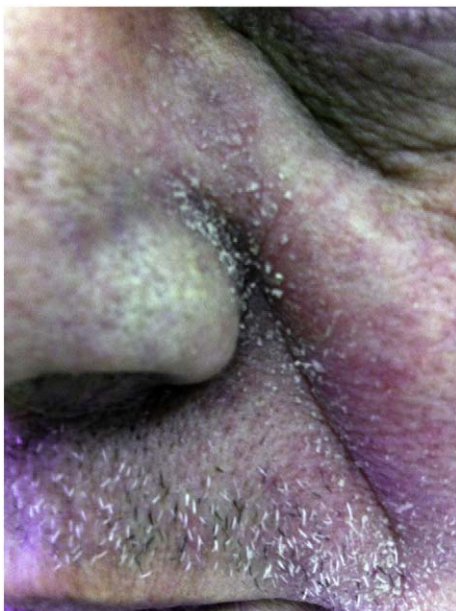


Fig. 8 Seborrheic dermatitis. Lateral view of the same patient seen in Figure 7.

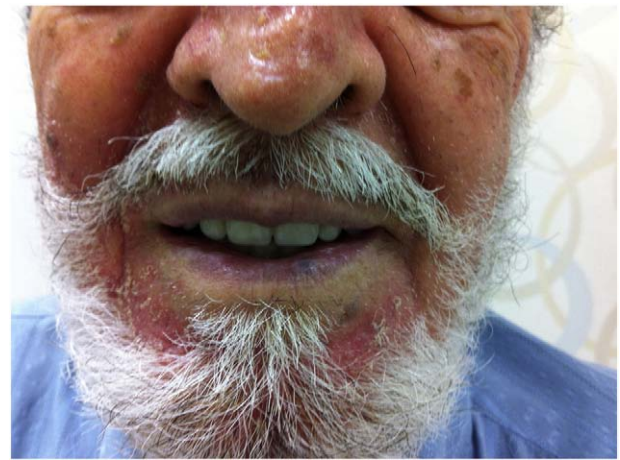


Fig. 9 Seborrheic dermatitis in the beard region.

folds in patients with SD and the extensor surfaces in patients with AD) and the frequent absence of itching with SD may differentiate these two diseases.

External agents

The evidence of a relationship between *Malassezia sp* and SD is the good responses that patients have to treatment with antifungal agents (eg, ketoconazole).^{24,27,28} It is known that *Malassezia sp* are found on the skin of all subjects, although historical studies disagree with regard to the amounts and the specific species that influence the appearance of SD.^{29–32} These findings suggest that physiopathological mechanisms other than quantity and quality are related to an abnormal reaction to *Malassezia sp* on the skin surface.

Local environment

The lipid composition of the skin surface favors the growth of *Malassezia sp* and thus the development of SD. *Malassezia sp* degrade lipids on the skin surface and produce unsaturated and saturated fatty acids that, when left in this environment, trigger an inflammatory response.^{28,33} Many studies demonstrate that there is no change in the humoral response to *Malassezia sp* but rather a change in the cellular immune response.^{34–36} Individuals with SD may have alterations in cellular immunity that predispose them to the development of the disease when they come in contact with *Malassezia sp*. Several studies did not find antibody production of immunoglobulins M and G against *Malassezia sp* in patients with SD, so there is no humoral immune response; this differs from what is found in the AD research, which states that some patients have antibodies against *Malassezia sp*.^{34–36}

Skin colonization by *Malassezia sp* in patients with SD is the result of an altered cellular immunity, which may be induced by the increased secretion of interleukin 10.³⁵ An increase in the number of NK1+ and CD16+ cells has been

found in some patients, which denotes the presence of a nonimmunogenic irritative stimulus.³⁷ These findings are corroborated by another study that suggests that *Malassezia sp* cannot release a stimulator factor for cytokine production by human keratinocytes and that cell-to-cell contact between *Malassezia* yeasts and human keratinocytes plays an important part in the cytokine production of human keratinocytes.³⁸

Genetics

The evidence cited by many authors to support the idea that there is some individual susceptibility that contributes to the development of SD does not specify the genetic mechanism involved.³⁹ The last study in this field was

performed in 1976 with the use of an old serological methodology for human leukocyte antigen typing, and it found HLA-AW31 and HLA-B12 to be associated with SD.⁴⁰ Our study group recently found a statistically significant association between SD and HLA A*32 and HLA B*18.⁴¹

It is currently believed that the factors that predispose individuals to SD are the presence of *Malassezia sp* on the skin and the metabolism of this fungus; the affected individual's susceptibility (ie, immunological profile and heredity); and the production of lipids on the surface of the skin.³⁹ The "outside-inside" theory extrapolated from AD can be used to discuss how an external factor (ie, *Malassezia sp.*) interacts with the local environment (ie, the oily skin and the altered cellular immunity) under specific circumstances (ie, individual susceptibility, genetics) (Figure 10).

SEBORRHEIC DERMATITIS

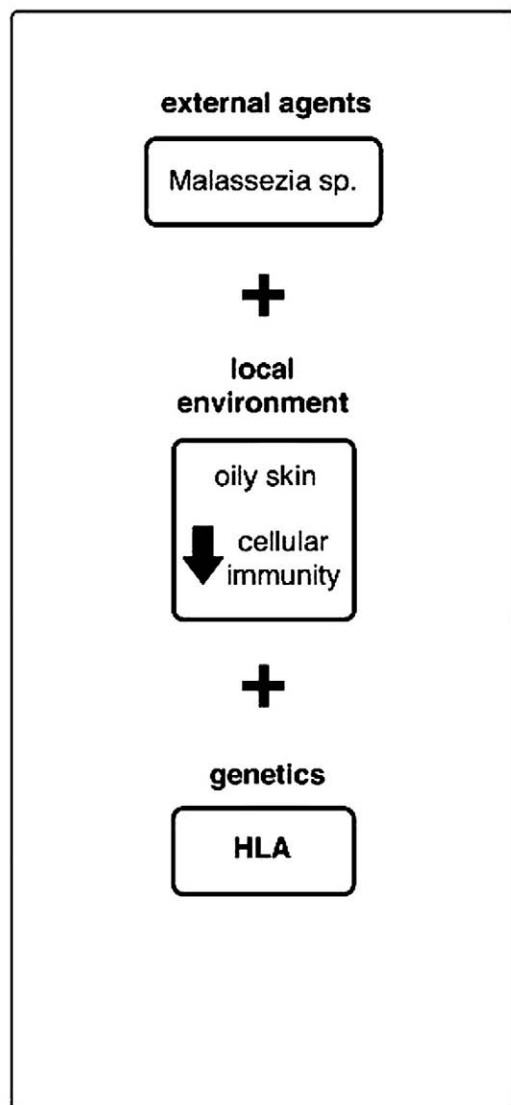


Fig. 10 Predisposing factors for seborrheic dermatitis.

Conclusions

Both AD and SD have some endogenous and exogenous triggering events, but neither condition can develop without a genetic predisposing factor. Both diseases depend on individual susceptibility. There are two points of view regarding the development of AD: the "inside-outside" theories and the "outside-inside" theories. In either case, all relevant factors have to be present for the disease to occur. With SD, inside and outside factors have been recognized, and the most important factor that remains is the quantification of the role of *Malassezia sp* in the clinical and pathological aspects of the disease. The search for the relevant genetic markers will be useful to obtain additional and improved knowledge about the peculiarities of SD and AD.

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