The primary mechanisms underlying atopic dermatitis

Les principaux mécanismes sous-jacents à la dermatite atopique

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Abstract

Introduction: Atopic dermatitis (AD) is a complex skin disease frequently linked with other atopic symptoms such allergic rhinitis and asthma. The disease's history consists of persistent relapses with extreme pruritus, which lowers quality of life. AD has become a global health concern as its incidence has increased over the last few decades. It ranks as the third most common dermatologic disorder.
Aim: There are several open questions about the mechanisms underlying atopic dermatitis (AD), This review aims to emphasize the recent advances in scientific research regarding the pathophysiologic mechanism of AD and the clinical application of these factors.
Methods: A PubMed search was performed using the keywords "Atopic Dermatitis (AD)", "epidemiology", "clinical presentation", "diagnosis", "pathophysiology", "genetic defect", "impaired skin barrier", "immune dysregulation". The search strategy included meta-analyses, clinical trial, observational studies, and reviews.
Results: Atopic dermatitis affects over 2 million children worldwide, with a lifetime incidence of up to 20%.
New data suggest that its incidence is still growing, particularly in low-income nations. AD is diagnosed clinically using the patient's medical history, particular clinical symptoms, and the elimination of other non-inflammatory skin conditions. The pathogenesis of AD is extremely complicated and involves several etiologies, including genetics, the microbiome, abnormalities in the skin barrier, along with dysfunctional innate and adaptive immune systems.
Conclusion: Recent research has improved our understanding of disease pathophysiology in atopic dermatitis.
Current and future clinical trials are expected to continue clarifying this complex and heterogeneous skin disease, and to develop medications that promise more effective therapy, particularly for individuals with limited response to conventional treatments.

Key words: Atopic Dermatitis (AD), clinical presentation, diagnosis, pathophysiology, genetic, treatment.

Résumé

Introduction: La dermatite atopique (DA) est une maladie cutanée complexe souvent associée à d'autres symptômes atopiques tels que l'asthme et la rhinite allergique. L'historique de la maladie est caractérisé par des rechutes persistantes avec un prurit intense, ce qui diminue la qualité de vie. La DA est devenue un problème de santé mondial car son incidence a augmenté au cours des dernières décennies. Elle se classe comme le troisième trouble dermatologique le plus fréquent.
Objectif: Plusieurs questions restent ouvertes concernant les mécanismes sous-jacents de la dermatite atopique (DA). Cette revue vise à mettre en évidence les récents progrès de la recherche scientifique concernant les mécanismes physiopathologiques de la DA et l'application clinique de ces facteurs.
Méthodes: Une recherche PubMed a été effectuée en utilisant les mots-clés « Dermatite Atopique (DA) », « épidémiologie », « présentation clinique », « diagnostic », « physiopathologie », « défaut génétique », « barrière cutanée altérée », « dysrégulation immunitaire ». La stratégie de recherche comprenait des méta-analyses, des essais cliniques, des études observationnelles et des revues.
Résultats: La dermatite atopique touche plus de 2 millions d'enfants dans le monde, avec une incidence au cours de la vie pouvant atteindre 20 %. Des données récentes montrent que sa prévalence continue d'augmenter, notamment dans les pays à faible revenu. La DA est diagnostiquée cliniquement en utilisant les antécédents médicaux du patient, des symptômes cliniques spécifiques en éliminant d'autres affections cutanées non inflammatoires. La pathogenèse de la DA est extrêmement complexe et implique plusieurs étiologies, notamment la génétique, le microbiome, des anomalies de la barrière cutanée, ainsi que des systèmes immunitaires innés et adaptatifs dysfonctionnels.
Conclusion: Les recherches récentes ont considérablement élargi notre compréhension de la pathogenèse de la dermatite atopique. Les essais cliniques actuels et futurs devraient continuer à clarifier cette maladie cutanée complexe et hétérogène, et à développer des médicaments promettant une thérapie plus efficace, en particulier pour les individus ayant une réponse limitée aux traitements conventionnels.

Mots clés: Dermatite Atopique (DA), présentation clinique, diagnostic, physiopathologie, génétique, traitement.

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Introduction

Atopic dermatitis (AD) or atopic eczema, is a chronic, inflammatory skin disease related with cutaneous hyperreactivity and induced by environmental variables(1). Dry skin, pruritus, lichenification, and recurrent eczematous abrasions are characteristics of AD(2). Dermatitis is derived from the Greek words "derma," meaning skin, and "itis," meaning inflammation, atopy is defined as genetic predisposition to generate immunoglobulin E (IgE) antibodies in reaction to minimal exposure to common environmental proteins like pollen, and food allergens(3).

AD occurs worldwide, with varying frequencies depending on the country and ethnic origin(4). While it appears to have stabilized in developed countries, AD prevalence appears to be growing in developing countries, most likely due to increased urbanization, pollution, and obesity(5,6). The beginning of AD typically manifests within the initial years of life in approximately 80% of individuals(7), and around 60% of those affected experience remission during adolescence(8).

Recently, it was demonstrated that the development of atopic dermatitis (AD) entails a complex interaction among immune dysregulation, genetic predisposition, environmental exposures, and disruption of the skin barrier(9). Despite certain limitations, the growing understanding of the immunopathogenesis of atopic dermatitis (AD) has led to the creation of innovative, highly effective, and well-tolerated medications(10).

This document provides an overview of epidemiology, clinical presentation, diagnosis, pathophysiology, and present also new developed therapies for this disease.

Epidemiology

Understanding the occurrence and prevalence of AD among various age groups and geographic areas is crucial for patient education and the distribution of healthcare resources(11). According to the WHO Global Burden of Diseases initiative's statistics, dermatitis atopic affects at least 230 million people globally, making it the greatest source of the non-fatal illness burden among skin disorders(7,12).

Based on a prior multinational epidemiological study involving adults, the point prevalence of diagnosed atopic dermatitis (AD) varied between 2.1% and 4.9% throughout nations(13).

In Africa, eczema prevalence varies from 4.7% to 23.0%, with notable differences between neighboring countries and even among cities within the same country(14). Generally, eczema rates are higher in countries across Africa and Oceania, whereas countries in the Indian subcontinent and Northern/Eastern Europe tend to have lower rates(4). The prevalence varies also across age range and according to some recent studies, AD affects 15–30% of children and 5–10% of adults, with a 2- to 3-fold increase in industrialized nations in recent decades(5,15). AD can be presented at any age but early childhood is when the disease mostly manifests, the incidence peaks are presented in the below graph(16) (Figure 1).

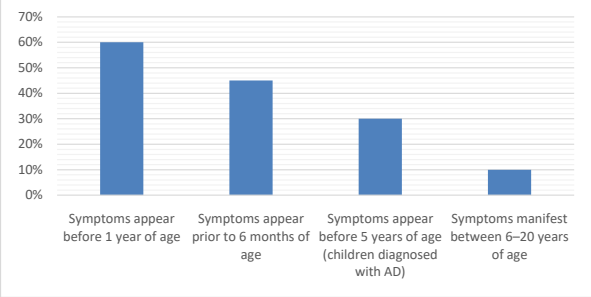

Figure 1. Approximate Distribution of Age at Onset for Symptoms of Atopic Dermatitis

Over a seven-year period, the lifetime prevalence of dermatitis atopic symptoms in 13 to 14-year-old children in Morocco, South Africa, and Kenya nearly quadrupled(17). In sub-Saharan Africa and the Maghreb, a study was carried out in 2019 on 69 patients for a period of 5 months, showed that the clinical signs of AD began in infancy for nearly half of the participants, among the 21 adults included in the study, the clinical signs of AD had an adult onset in 61.9% of them (18).

Clinical presentation and diagnosis

The clinical presentation of Atopic Dermatitis (AD) varies significantly with the patient's age(15), There are at least four distinct clinical types: infantile, childhood, adolescent/adult, and elderly(19). Clinical manifestations are summarized in Table 1.

Table 1. Clinical manifestations of AD(20–22).

Infants (0–2 years)	Childhood (2 years to puberty)	Adolescence/ adulthood	Elderly
-Extensor surfaces of extremities, -Face (forehead, cheeks, chin) -Neck, -Scalp, -Trunk.	-Flexural surfaces of extremities, -Neck, -Wrists, -Ankles.	-Flexural surfaces of extremities, -Hands, -Feet.	-Extensive eczematous lesions up to erythrodermic aspects with a strong pruritic component, -Sometimes the lesions spare the flexural areas.

Since AD and other eczematous conditions, as contact dermatitis, have histological similarities, the clinical criteria, including the UK Working Party criteria and the Hanifin and Rajka criteria, are now used to diagnosis AD(10). Williams and colleagues created simplified criteria for the diagnosis of AD that are easy to use, do not involve intrusive testing, and have been proven to have excellent sensitivity and specificity(23), more details are described in table 2. Apart from the traditional diagnostic standards, the severity of Atopic Dermatitis is best assessed with verified scoring systems, such as EASI (Eczema Area and Severity Index), SCORAD (Scoring Atopic Dermatitis), IGA (Investigator global assessment), NRS (Pruritus numerical rating scale) (19,24).

Table 2. Diagnostic criteria for AD(21,22).

Major criteria	Minor criteria (Plus three or more of the following minor criteria)
Patient must have an itchy skin condition (or parental/caregiver report of scratching or rubbing in a child)	**Older children/adults** • History of involvement of the skin creases such as folds of elbows, behind the knees, front of ankles, around the neck, • Personal history of asthma or hay fever, • Personal history of general dry skin in the last year, • Visible flexural eczema, • Onset under age 2 years, **Children<4 years*** • History of itching of the cheeks, • History of atopic disease in a first-degree relative, • Eczema of cheeks, forehead, and outer limbs.

* Early onset not always diagnostic in children under 4 years of age

Pathophysiology

The pathophysiology of AD is very complex and involves the combination of several factors(23).
To explain the inflammatory sores in atopic dermatitis, many theories have been suggested. AD's etiology appears to be driven by the reciprocal interaction between disturbed skin barrier, the skin microbiome, immunological dysregulation, among persons with susceptibility genes for AD and environmental factors(25) (Figure 2). In fact the polymorphisms of genes associated with both innate and adaptive immunity, particularly those linked to Th2 signaling pathways, have also been implicated in the pathogenesis of AD(26). These theories are not mutually exclusive, they may be complementary with further research.

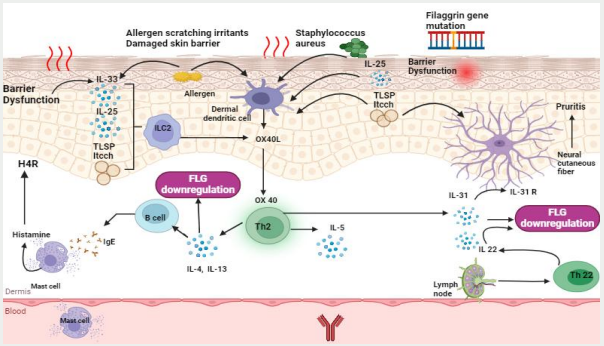

Figure 2. Pathogenesis of atopic dermatitis.

FLG; filaggrin, **Th2 cell**; T helper type 2 cell, **Th22 cell**; T helper type 22 cell, **IL**; interleukin, TSLP; thymic stromal lymphopoietin, **IgE**; immunoglobulin-E, **H4R**; histamine-4 receptor, **ILC2**; group 2 innate lymphoid cells.

Barrier-disrupted keratinocytes exhibit strong production of immunoregulatory cytokines like thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 collectively activate innate lymphoid cell-2 (ILC-2) to express OX40L, which in turn triggers the activation of Th2 cells. Dendritic cells (DCs) are stimulated by TSLP and IL-25 to express OX40L. The interaction between OX40L and OX40 triggers the onset of type 2 immunological differentiation of T cells. Th2 cells express IL-13, IL-4, IL-5, and IL-31. IL-13 and IL-4 impair barrier function by inhibiting FLG expression, while IL-22 also reduces FLG expression. Furthermore, IL-31 decreases the expression of FLG and induces itching by activating sensory nerves. This itching leads to increased barrier disruption and facilitates the entry of allergens into the skin and encourages colonization by Staphylococcus aureus. This process releases inflammatory substances such as histamine and leads to increased levels of IgE. Additionally, IL-4 and IL-13, increase B cell IgE class switching and antigen-specific IgE molecule synthesis(27–29).

Genetic defect

An increased frequency of AD in families with a history of atopy raised first questions regarding the genetic basis of atopic dermatitis(30). It was observed that children whose parents have a background of allergic diseases are more likely to acquire AD(31). Observational studies were the first to demonstrate a key risk factor for atopic dermatitis, indicating a prevalent positive family history among AD patients and in twin investigations, demonstrating that monozygotic twins have a greater concordance rate than dizygotic twin (32). When analyzing the morbidity of monozygotic and dizygotic twins, the risk of dermatitis atopic was estimated to be 72-86% and 21-23%, respectively(33). Furthermore, genetic studies have revealed 31 distinct chromosomal regions including genes associated with AD risk(34). Also, recent studies suggest that more than 70 genes may be connected to AD in various groups(35). The predominant genes encode proteins that control both acquired and innate immune responses, along with genes responsible for functional and structural proteins in the epidermis (table 3), such as the filaggrin (FLG) gene(35). The FLG gene is situated on chromosome 1q12 within the epidermal differentiation complex (EDC), where it plays a role in encoding filaggrin, a vital structural protein essential for the integrity of the stratum corneum (SC) (4). The epidermal differentiation complex (EDC) comprises 27 genes, with 14 of them being expressed in the final stages of keratinocyte development(36). The remaining 13 genes in the EDC encode proteins expected to function as signal transducers during the processes of keratinocyte and other cells and tissues(32). R501X, 2282del4, S3247X, and R2447X are the most common FLG loss-of-function mutations, present in 7%–10% of white Europeans; R501X and 2282del4 mutations are the most frequent in Europeans(37,38). Both the R501X mutation and the 2282del4 mutation are highly indicative of AD and this association was also reported in a population of African ancestry(39).

Among the 31 gene loci linked to AD in meta-analyses of genome-wide association studies, FLG, OVOL1, and IL-13 are the top three significant genes. Null mutations in the FLG gene are the most powerful risk factors for AD (34).

Table 3. Main groups of genes linked to the development of atopic dermatitis AD(40–45,45–55).

The pathological mechanisms involved in atopic dermatitis (AD)	Example of Genes Involved
Epidermal barrier genes	-Filaggrin, filaggrin 2, hornerin Cornodesmosomal genes (desmoglein, desmocollin) and tight junction genes (claudins, occludins), -Epidermal protease genes (kallikreins, cathepsins, caspase 14), along with their inhibitors (SPINK5, Cystatin A) OVOL1 (ovo-like transcriptional repressor) – a transcription factor that regulates FLG expression.
Genes of the innate immune mechanisms	-TLR1, TLR2, TLR4, TLR6, TLR9, TLR10, CD14, NOD1, and defensins (DEFB1). -Genes encoding receptor subunits for IgE, -Genes involved in the Th2 response: IL-4, IL-5, IL-13, IL2RA, IL-13RA, IL-5RA, and TSLPR.
Genes of the adaptive immune mechanism	-IL-4R, IL-18, IL-31, and additional genes associated with T-helper cell bias such as IL17A, TNFα, and IL-22, -Genes related to regulatory T cells (Tregs) include STAT-6, FOXP3, and LRRC32.
Genes encoding alarmins produced by keratinocytes	IL-25, TSLP, IL-33.
Genes regulating DNA methylation	KIF3A

Impaired skin barrier function

An intact epidermal barrier is a prerequisite for the skin to function as a physical and chemical barrier. Genetically determined alterations of the epidermis or lipid composition contribute to skin barrier dysfunction leading to inflammation(5). The primary medical co-morbidities associated with AD are microbial infections, particularly those caused by Staphylococcus aureus(56,57). It is well established that S. aureus colonizes the skin of 60% to 100% of atopic dermatitis patients, whereas this occurs in only 5% to 30% of healthy individuals(58–62). According to a meta-analysis, S. aureus colonization is observed on both lesional and non-lesional skin, as well as in the nasal passages, S. aureus carriage rates are 70% on lesional skin, 39% on non-lesional skin, and 62% in the nasal area among AD patients(63).

In fact, S. aureus inhabits the skin and generates virulence factors which cause inflammation and skin barrier failure in AD (64). This phenomenon is attributed to the activity of wide range of toxins and superantigens in S. aureus (65). Changes in the pH level toward more alkaline are the one of the variables that facilitate S. aureus colonization and proliferation in AD patients(66–68). Lower pH levels are associated with decreased expression of proteins, particularly those implicated in S. aureus skin adhesion(69). Individuals with a mutation in the filaggrin gene (FLG) exhibited higher levels of S. aureus colonization compared to those with the wild-type gene(70). Factors such as exposed bacterial binding sites in the extracellular matrix, abnormalities in innate immunity, and dysfunction in cellular immunological responses with predominant Th2 responses are likely contributors(71,72).

Immune dysregulation

Innate lymphoid cells type 2 (ILC2) are recognized for their capability to produce cytokines, such as IL-4, IL-5, IL-9, and IL-13(36). In fact, IL-33 and IL-25 activate ILC2 cells and promote Th2 responses by enhancing their secretion of IL-13 and IL-4(73). Additionally, IL-4 and IL-13 amplify IL-31-mediated sensory nerve signaling(29). Furthermore, IL-4 and IL-13 inhibit the synthesis of filaggrin in keratinocytes, aggravate epidermal barrier failure, and increase eosinophils and IgE antibodies in peripheral blood and tissues(74).

T helper type 2 cells release IL-31, which is overexpressed in pruritic skin compared to non-pruritic skin(75). It has been observed that IL-31 stimulates sensory nerve elongation and branching, which supports its function of sensitivity to minimum stimuli and prolonged itch in individuals with AD(76).

The pathogenesis of AD is not solely attributed to Th2 immunity; IL-17 has also been implicated in reducing the expression of FLG(77,78). Th17 cells generate both IL-17 and IL-22, while Th22 cells primarily release IL-22, increased levels of IL-22 in the serum of patients with AD have been linked to the severity of the disease(10). Significantly, all these data and new updates have aided in the creation of novel treatments that have either received approval or exhibit promise in clinical studies(79).

Treatment of atopic dermatitis

The main objectives in treating atopic dermatitis are to minimize pruritus and maintain durable disease management that allows patients to be completely functioning at home, work, and school(7).

The choice of therapy depends largely on the severity of the illness. For the majority of individuals with mild-to-moderate illness, topical treatment with corticosteroids or calcineurin inhibitors is adequate(80). However, some individuals, despite standard therapy, continue to have problematic AD and poor quality of life, these patients should be evaluated for second-line therapy, including immunosuppressive medicines and phototherapy(81). Recently, the food and drug administration have approved new targeted medications for both children and adults(82). The mechanisms of action of novel medications for atopic dermatitis (AD) can be classified into biologics and small molecules (table 4). Biologics, including monoclonal antibodies, are characterized by their high selectivity for specific molecular targets, such as interleukins or their receptors, small molecules that disrupt cellular downstream communication to reduce the production of a wider variety of proinflammatory components(10).

A deep understanding of the complex pathophysiology of AD is essential for identifying new treatment targets.

Translating this knowledge, including key pathways and potential treatments, into drug development has led to significant advances in both preclinical and clinical

research(94).

Table 4. Example of some current therapeutic pipeline for atopic dermatitis.

Agent	Target	Route of delivery	Category	References
Dupilumab	IL-4Rα	Injection	Biologic	(83,84)
Nemolizumab	IL-31R	Injection	Biologic	(85)
Lebrikizumab	IL-13	Injection	Biologic	(86)
Tralokinumab	IL-13	Injection	Biologic	(87)
Secukinumab	IL-17	Injection	Biologic	(88)
Tezepelumab	TLSP	Injection	Biologic	(89)
Etokimab	IL-33	Injection	Biologic	(90)
Fezakinumab	IL-22	Injection	Biologic	(91)
Mepolizumab Benralizumab	IL-5	Injection	Biologic	(92–94)
Abrocitinib	JAK 1	Oral	Small molecule	(10,27)
Upadacitinib	JAK 1	Oral	Small molecule	(10,94)
Baricitinib	JAK1/JAK2	Oral	Small molecule	(27)
Ruxolitinib	JAK 1 /JAK 2	Topical	Small molecule	(95)
Delgocitinib	JAK 1, JAK 2, and JAK 3 and tyrosine kinase 2	Topical	Small molecule	(96,97)
Brepocitinib	JAK1/TYK2	Topical	Small molecule	(27)

In General, AD presents a complex clinical profile, involving a range of overlapping factors in its pathophysiology. Both T and B cells, along with their associated cytokines, contribute to this disease's immunological profile, this is marked by a dominant Th2 axis (involving IL-31, IL-13, IL-4, IL-5, and TSLP), elevated Th17/IL-23, Th22 pathways, and increased IgE levels(94). Additionally, disruptions in skin microbial diversity, notably the overabundance of Staphylococcus aureus strains, further emphasize the complexity of AD's etiology(98).

Indeed, the Th2 pathway represents a valuable therapeutic target, with IL-31 playing a significant role in the persistent itch-scratch cycle associated with AD(99). Nemolizumab is monoclonal antibody developed for targeting the IL-31 receptor α (IL-31Rα) by binding to IL-31Rα on immune cells, keratinocytes, or nerve fibers(100).

IL-4 and IL-13 are recognized as key drivers of the Th2 immune response(94). Tralokinumab works by inhibiting IL-13 from binding to its receptors, IL-13R1 and IL-13R2. In a similar fashion, lebrikizumab selectively targets IL-13, preventing the heterodimerization of IL-13Rα1 and IL-4Rα, thereby disrupting the subsequent signaling cascade and ultimately halting the progression of AD(101,102). Both Lebrikizumab and Tralokinumab have shown considerable effectiveness in the treatment of moderate to severe AD(103).

IL-4R also represents an excellent therapeutic target due to its role in facilitating IL-4 and IL-13 signaling. The FDA approved dupilumab for the treatment of AD in patients aged six months and older(104). Dupilumab inhibits the mRNA expression that triggers T cell activation, inflammatory cascades, eosinophils, dendritic cells, and Th2 cytokines(105).

In AD patients, blood eosinophil levels are typically higher. Benralizumab and mepolizumab suppress the function of IL-5 by inhibiting the IL-5 receptor(94). Mepolizumab significantly reduced the quantity of peripheral blood eosinophils during 16 weeks of treatment(94). However, the drug failed to demonstrate a significant decrease in the SCORAD(27) and it did not meet the primary goals of clinical improvements(92).

For several cytokines, including interleukins like IL-4, IL-13, and IL-31, the JAK/STAT signaling pathway serves as a classical cascade(106). The JAK family of tyrosine kinases comprises four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)(107). Recently, three JAK inhibitors, upadacitinib, abrocitinib, and baricitinib, have been approved to treat AD(94).

Targeting the Th22 pathway as a therapeutic strategy is also promising, IL-22 is highly elevated in the lesional skin of patients with AD and is strongly associated with disease severity(108). IL-22 plays a crucial role in promoting keratinocyte proliferation and downregulating filaggrin expression(109), making it an attractive target for AD treatment. Fezakinumab, an anti-IL-22 therapy, can be used to inhibit IL-22 and potentially improve disease outcomes(27).

Recent breakthroughs in the pathophysiology of AD have significantly enhanced therapeutic outcomes. These new therapies have transformed the management of AD, allowing patients who previously showed no response to traditional treatments to achieve successful results(94).

Conclusion

The elevated incidence of AD in developing countries has been a major public health problem as AD is linked to a wide range of physical and mental health conditions. The disease can persist, significantly affecting a patient's quality of life. Managing the costs related to AD can be challenging for both the patient and their family. In the past three decades, there has been significant progress in understanding the pathophysiology of AD. Emerging innovative therapies have been made possible by these new understandings of the effects that are connected to genetics and immunity. With a diverse range of medications, patients might be treated according to their dominant Th2, Th22, or Th17 immunotypes or if a filaggrin mutation is present or absent.

Prompt diagnosis and treatment might potentially reduce the disease's morbidity and prevent its progression to other associated atopic conditions. Future research still really needed to focus more on exploring gene-environment interactions and its effect on pathophysiology, disease severity, and treatment outcomes.

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