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Disease Review

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Atopic Dermatitis: Treatment Practices And Prevention- The Ayurvedic Way

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Abstract

Atopic dermatitis (AD), collectively known as eczema, is a chronic inflammatory skin disease that is characterized by a dysfunctional skin barrier. AD, also called atopic eczema, is a recurrent inflammatory skin condition that affects 15-20% of children and 1-3% of adults worldwide. It is a chronic condition characterized by acute flare-ups of eczematous pruritic lesions that causes the skin to become inflamed and irritated. Sadly, the prevalence of this disorder is increasing, and it poses a significant burden on health-care resources and patients' quality of life. It is evident that dermatologists have many treatment options and guidelines for AD. Still, the treatment does not seem to address AD individuals' underlying issues, as they vary from patient to patient. Several patients and families with AD are seeking a more holistic approach to help address and find a cure for the disorder. There is an increased emphasis on natural therapies, and alternative medicines such as Traditional Chinese Medicine (TCM), acupuncture, and Ayurveda, in conjunction with Western medical treatments are being pursued. This review attempts to summarize some of the available treatment options to understand the integrative holistic approach needed to treat an AD individual.

Keywords: eczema, atopic dermatitis; Ayurveda

Introduction:

Atopic dermatitis (AD), collectively known as eczema, is a chronic inflammatory skin disease that is characterized by a dysfunctional skin barrier.[1] The word eczema comes from the Greek word *ekzein* meaning "to boil out"; word *ek* means "out", while *zema* means boiling.[2] The exact cause of eczema is not known. People with eczema do have the IgE antibodies (immunoglobulin E) produced by the immune system as part of allergic reactions. Eczema

can be a tough and vexing condition accompanied by overwhelming psychological challenges faced by the patients. AD is a chronic condition that causes the skin to become inflamed and irritated, making it extremely itchy. It can come and go for years or throughout life and can overlap with other types of eczema. The disorder is often observed to be associated with redness, swelling, ''weeping'' clear fluid, crusting and scaling.

AD is a common condition and anyone can get the disease, but it is commonly seen to begin in childhood. Living with atopic dermatitis can often be arduous, but treatment can help control symptoms. In United States (US) and Europe, the prevalence of AD among children is estimated to be approximately 20%, and among adults is estimated to range between 7% and 14% in adults. The condition is extremely widespread in the US, and it is estimated that over 31 million Americans suffer from some type of eczema. In the US, AD is the most common type of eczema, affecting over 9.6 million children and about 16.5 million adults. An estimated $364 million to $3.8 billion is spent on treating and managing AD each year.[3] It therefore accounts for a significant economic global burden.[4] among skin disease treatments.

In approximately 80% of affected individuals[2], eczema can begin during childhood. However, it can also begin during adolescence and even in adulthood; the disorder can range from mild to severe.[5] AD is typically considered the first step of the 'atopic march', associated with a risk of developing asthma, or food allergy.[6] The lipid barrier of skin is generally reduced in people suffering from eczema, compared to people who do not have the disorder. Trans epidermal water low (TEWL) from the skin is also common, leading to a dry and compromised skin. Once the skin barrier is compromised, different irritants and materials can easily penetrate the skin and make it vulnerable to infections. The immune system also overreacts to environmental allergens and causes inflamed, irritated, or sore skin.[7] ''Itch that rashes'' is characteristic feature of eczema.[8]

An agreement seems to exist among the research community that the cause of AD is due to a combination of both genetic and environmental factors. Genes responsible for encoding protein S100, or filaggrin, proteases and their inhibitors have been studied extensively and have been found to be associated with AD especially with epidermal barrier dysfunction.[1] These genes are involved in altering the normal skin function in a myriad of ways. In addition, these genetic predispositions are interpreted as leading to an increase in probability of developing atopic dermatitis if one of the parents suffers from it.[9] A recent study correlated

the defects in the filaggrin gene to eczema and asthma.[10, 11] Advanced genetics methods such as genome-wide association (GWA) and single nucleotide polymorphism (SNP) have been employed to directly associate AD with genes of innate/adaptive immune systems, human leukocyte antigens (HLA), cytokines, chemokines, drug-metabolizing genes and various other genes.[11] A number of environmental triggers and causes such as allergens, poor hygiene, and diet have also been attributed to dysfunctional skin barrier.[12]

Treatment of this condition usually begins through a self-assessment followed by a diagnosis by a physician or a dermatologist. Patients are often recommended to avoid allergens that may trigger an inflammatory response and to further avoid any itching that may lead to a compromised skin barrier. Topical steroids, antihistamines, and emollients are some of the common medications prescribed to treat eczema.[13]

Outside of Western medicine, the use of alternative therapies such as Chinese herbal preparations, homeopathy, yoga, Ayurveda, or massage therapy as a complementary therapy (or an integrative method) to manage AD/eczema symptoms is growing. Ayurveda, a traditional holistic form of medicine that began in India seeks to bring the mind, body, and soul into balance by employing herbs, oils, diet, massage, and mind-body practices like yoga and meditation to balance the life humors, or *doshas*. Ayurveda believes that good health is the result of three humors or forces of the body being in balance, and diseases happen when they are out of balance. The three *doshas* are called *vata, pitta,* and k*apha*.

Ayurveda describes skin diseases as *twak rogas* or *kushtha* and eczema as a type of *kshudra kushtha,* or minor skin ailments.[2,14,15] Ayurveda describes eczema as a group of inflammatory conditions which can be either acute or chronic. Different causes for the disorder are described and various configurations have been reported. Acute eczema is usually seen as a rapidly evolving, red, blistered, and swollen rash while chronic eczema is a long term, irritated, sensitive, thickened, lichenified often accompanied by puritic skin.[16] Based on the presentation, Charaka and Sushruta correlate eczema with *Vicarcika*.[17,18] According to

सकण्डूः पिडका श्यावा बहुस्रावा विचर्चिका||२६||

The clinical features of Vicharchika

- **Color** – blackish brown
- **Nature** –excessive exudation, eruptions
- **Associated symptoms** – pruritus

https://www.carakasamhitaonline.com/index.php/Kushtha_Chikitsa, 2.6.1111.*Vicārcikā kuṣṭha*

Charaka, *Vicarcika* is caused by an increase in *kapha* and reduced blood supply, leading to blackish brown discoloration which is further accompanied by obstructive changes. These later affect the local immunity and gives rise to a chance for dermatophytes to penetrate the skin barrier. This results in eruptions, thereby causing excessive exudation. Secondary infection and reduced blood supply leads to pruritus. This condition is often compared with wet eczema.[17] *Vicarcika* or eczema, is also described as '*Rakta Pradoshaja Vikara'* meaning that it has involvement of all the three doshas, with *kapha* playing a dominant role.[19,20,21] In addition, Sushrata Samhita describes *Vicarcika* as psoriasis, and eczema is described as small pustules or pimples characterized by an itching, burning secretion and appearing on the surface of the body; these are also termed *Fakma* (eczema).[18] Eczema flares happen frequently in these patients; therefore, finding a treatment plan that manages these flares is important for the wellbeing of the patient.[20] Charaka has mentioned that in all the chronic diseases, regenerative *rasayana* drugs can be prescribed to help build *rasa* and *dhatus* i.e., body cells and tissues.[22]

Western Medicine Perspective

AD is a multifactorial disease with genetics playing an important role in the presentation of the disorder, and filaggrin's role in skin barrier impairment in the development of AD is well documented. In addition, environmental factors and microbial involvement are also recognized to play a role in the development of the disease. Western medicine focuses on mitigating the adverse factors that are known to cause the condition, with the help of pharmaceutical treatments. People with eczema tend to have an over-reactive immune system. When triggered by a substance inside or outside the body, the immune system responds by initiating inflammation. It is this inflammatory response that causes the itchy, painful, rash-like symptoms common to several types of eczema. Unfortunately, AD usually presents itself in early childhood; within children, its prevalence is 20% and continues to rise globally.[10] It is a complex disease, affecting all strata of life alike.[9, 23]

Types of Eczema

There are seven primary forms of eczema (Table 1), each with different triggers, symptoms, and treatments.

Table 1: Types of Eczema

	Type	Symptoms	Treatment
1	Atopic dermatitis	This is the most severe and long-lasting form of eczema. It's characterized by inflamed skin that may crack and release a clear fluid when scratched (an effect known as "weeping").[24] The patches are often infected with *Staphylococcus aureus* (staph)	Avoiding triggers, stress, and maintaining a good routine and lifestyle. Topical corticosteroids, non-steroidal topicals and biologics are often used. Often antimicrobial treatments are needed. The allergens need to be addressed
2	Contact dermatitis	This is an allergic or the irritant kind of skin flare up; it is usually localized. The irritant contact dermatitis accounts for about 80%.[25] This kind does not run in families and is not linked to other allergic conditions such as hay fever or asthma.	Steroids
3	Neurodermatitis	Is a common type of eczema that affects about 12% of the population with intense itching and scratching along with symptoms of neurodermatitis, In some cases itching is related to pleasure. [26] Chronic scratching causes itchy patches of skin to become dry, leathery and thickened known as *lichenification*, and neurodermatitis is also known as lichen simplex chronicus.	Corticosteroids, calcineurin inhibitors and salicylic acid ointments, zinc oxide paste, medicated patches that contain lidocaine, oral medications such as antihistamines, colloidal oatmeal, and lifestyle changes, including yoga, and relaxation technique.
4	Dyshidrotic eczema	This form is more common in people who suffer forms of eczema. It likely has a genetic component and presents as small and itchy blisters on the palms of hands, soles of feet, and edges of the fingers and toes. The cause of dyshidrotic eczema is not known, though a fungal component is	Staying away from triggers, preventing stress, having a regular skincare routine. Use ceramides based topicals to help repair the skin barrier, topical corticosteroids, cool compress, and anti-fungal medication. Prescribe light therapy, topical calcineurin inhibitors

		suspected. Risk of bacterial infections is also present.	(TCIs) or oral steroids. Botulinum toxin injections are used in extreme cases
5	Nummular eczema	Scattered circular, itchy, and sometimes oozing patches are commonly seen in nummular eczema, or discoid eczema or nummular dermatitis,. The spots can look coin-shaped on the skin. Triggers can include very dry or sensitive skin and trauma to the skin from insect bites, scrapes or chemical burns. These patches are often infected with *Staphylococcus aureus* (staph)	It is often treated with a mid- or high-potency topical corticosteroid, and a topical antibiotic. Astringents can help dry the infected patches and reduce symptoms.
6	Seborrheic dermatitis	A chronic form of eczema, seborrheic dermatitis appears on the body where there are a lot of oil-producing (sebaceous) glands like the upper back, nose and scalp. It is most common in infants and adults between the ages of 30 and 60, and is more common in males. The condition is an inflammatory reaction to excess Malassezia yeast, an organism that normally lives on the skin's surface	Following a skincare routine and healthy lifestyle, managing stress, washing affected areas daily with a gentle, zinc-containing cleanser (2% zinc pyrithione) applying moisturizer. Mild cases can be helped with a topical antifungal cream or medicated shampoo, and for severe cases, intermittent use of a topical corticosteroid or calcineurin inhibitor may help.
7	Stasis dermatitis	This condition is due to poor circulation in the lower legs. It is known as stasis dermatitis, gravitational dermatitis, venous eczema, or venous stasis dermatitis. Venous insufficiency happens when the valves in leg veins are weak and fluid collects in the lower limbs due to leakage. Can be due to aging or other underlying diseases.	Treatment involves use of compression stockings to reduce swelling or elevating legs above the heart, avoiding foods high in salt, supplemental vitamin C, and rutin. To treat itchy skin, a topical corticosteroid to calm inflammation can be used, and topical or oral antibiotic is prescribed if skin is infected

[27]Source: https://nationaleczema.org/eczema/types-of-eczema/

It is possible to have more than one type of eczema at the same time. Each form of eczema has its own set of triggers and treatment requirements.

Pathophysiology- how much do we know?

Eczema or AD is a condition that causes a person to develop patches of dry, itchy skin on their body. It often develops as a result of inflammation in the body, so eating foods that do not result in inflammation may help reduce symptoms. It is a chronic ailment characterized by distinct flares and pruritus, altering between persistent flares with itching and complete remission. These can be very distinct and vary in intensity, frequency, and duration among individuals affected by AD. Over-the-counter creams and medications can help to reduce inflammation. Research to understand the causative factors of eczema, and to elucidate the genetics of AD has been an ongoing effort. The disease is highly complex and with involvement of multiple factors, the pathophysiology is still evolving, and a lot remains unknown. AD usually appears early in life. A constant interaction of a dysfunctional epidermal barrier and the environmental irritants dictate the development of the disease. The predisposed genetic factors also play a role in shaping the disorder. A primary immune dysfunction is suspected which results in IgE sensitization and allergic inflammation. A secondary epithelial barrier disturbance has been proposed and some are of the belief that a primary defect in the epithelial barrier leads to secondary immunologic dysregulation and later inflammation. Recent studies have also indicated that allergy in AD individuals could be due to the disease itself. A need exists to look for alternative ways of preventing the onset of AD.[28]

Mechanisms

In healthy individuals, balance between important subsets of T cells (eg, Th1, Th2, Th17, Th22 and a biphasic inflammation is seen. A Th2-biased immune response (IL-4, IL-13, including thymic stromal lymphopoietin (TSLP) and eosinophils is predominant in the initial and acute phase of AD, while a Th1/Th0 is prevalent in chronic AD skin lesions (IFN-γ, IL-12, IL-5 and GM-CSF).[27] It is proposed that a primary immune dysfunction may lead to an imbalance in the T cell subsets potentially increasing Th2 cells. The Th2 cells are known to influence a rise in type 2 cytokines such as interleukin IL–4, IL-5, and IL-13 which further trigger an increase in IgE from plasma cells. In individuals with chronic AD though, the Th1 cells have been shown to dominate and Th17 cells have been found to be elevated in patients with AD.[29] Eosinophils and mast cells have also been implicated in the pathogenesis of AD.[30] It has been implicated

that basophils and group 2 innate lymphoid cells (ILC2s) are regulated by a family of epithelial cell–derived cytokines which are released from damaged keratinocytes, including TSLP, IL-25, and IL-33. There are studies which indicate that a classical adaptive Th2 cell and innate type 2 immune cells both play a critical role in the etiology of AD through interactions with epidermal-derived cytokines. The innate immune system represents the first line of defense against infections. In AD, a decrease in the antimicrobial peptides has been seen, and in AD individuals, Staphylococcus aureus colonization is often detected.

Th2 cells are known to be significant sources of the itch-inducing cytokine or pruritogen IL-31.[31] A 2017 study identified that neuronal signaling of the type 2 cytokines IL-4 and IL-13 regulate AD-associated itch.[32] Dupilumab, a dual IL-4 and IL-13 monoclonal antibody (mAb) was developed and was approved in 2017 and has been advertised as a highly effective treatment for AD. The US Food and Drug Administration (FDA) approved dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults which is not managed with topical medications. It was the first biologic agent approved to treat AD. In October of 2018, Dupilumab received approval by the FDA as an add-on maintenance therapy in patients with moderate-to-severe asthma aged 12 years or older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. Dupilumab is an antagonist, works by binding to IL-4Rα, and further modulates signaling of both the IL-4 and IL-13 pathways. Dupilumab is given as a subcutaneous injection and works by targeting the Th2 pathway to inhibit the inflammatory responses that drives the symptoms of atopic dermatitis.[33]

AD individuals develop symptoms of AD as a result of skin barrier defects following entry of antigens or allergens, which further stimulates the inflammatory cytokines pathway. There is a possibility that antigens enter the system via the gut or the lungs as well. Xerosis and ichthyosis are known to be associated signs in many AD patients, and studies have shown that 37 to 50% of people with ichthyosis vulgaris have atopic disease and up to 37% of people with AD show clinical signs of ichthyosis vulgaris. Recent studies have shown a strong link between mutations in the gene encoding filaggrin (FLG), a key epidermal barrier protein, and ichthyosis vulgaris.[34] Critical components involved in establishing the skin barrier protection are in the outer layers of the epidermis, especially the proteins that form the tight junction (TJ) and components of the innate immune system. FLG is a key protein in the epidermis and for the formation of the skin barrier. FLG mutations have been associated with

early-onset AD.[9, 28, 35] Interleukins IL- 4 and IL-13 are found detected in AD lesions and have been shown to decrease expression of FLG in keratinocytes.[1] The family of IL-1 has relevant pro-inflammatory features, such as IL-1α, suggesting that the onset of inflammation may occur due to changes in the skin barrier. These patients with AD with a deficiency in FLG expression have decreased stratum corneum hydration, increased TEWL, and higher pH. Besides, inflammation, and reduced protein expression in keratinocytes could be related to FLG deficiency.[36] Over 100 genes have been identified to be associated with AD,[11,37, 38] including genes like SPINK5/LEKT1 and DNA methylation differences have also been linked with AD.[39,40]

AD exhibits a complex pathogenesis, compromised skin barrier, and an imbalance of the immune system. The protective components of the skin barrier are present in the outer layers of the epidermis including proteins such as FLG, the proteins that form the tight junction (TJ), and components of the innate immune system. Changes in skin barrier control the pathogenesis of AD, linking the structural changes with the innate and adaptive immune system. Potent, cost-effective and safer therapies are essential to prevent, manage and treat AD effectively.[36]

Treatment

Recommended first-line action to take to prevent AD flares involves reducing exposure to potential allergens such as dust mites or pollen. Other measures which are equally important for an AD individual is reducing dryness and developing good hygiene/skincare routine to reduce itchiness or infection. Some of the common medications that are used by Western Medicine for AD includes topical steroids, antihistamines, and antibiotics, calcineurin inhibitors, phosphodiesterase-4 (PDE4) inhibitors, moisturizers and barrier repair agents, and wet wraps. Topical steroids are among the most popular of these medications and have been heavily used for the past 40 years in the treatment of AD.[41] Most of them work by constricting blood vessels, thus lessening the inflammation of the skin and the redness associated with AD. Hydrocortisone was used first and since, many corticosteroid compounds have now been licensed for treatment of AD. The development of the topical immuno-modulators, tacrolimus and pimecrolimus are expensive and are not effective. Unfortunately,

this is not a safe solution, as it is well known that the long-term use of topical steroids can result in many side-effects, such as folliculitis, skin atrophy, striae, erythema, and infection.

Antihistamines are a common medication prescribed to prevent allergic reactions and intense itching for AD individuals. Itching is a common symptom in an inflammatory disease such as AD and can damage the skin barrier, causing additional dryness and potentially infection.[42] Itching is often caused by histamine, a molecule held accountable for triggering an inflammatory response. Therefore, antihistamines are commonly prescribed to reduce itching and associated inflammation, thereby preventing any secondary skin barrier damage.

Antibiotics are used to treat the symptoms associated with AD. They are usually prescribed to prevent and eradicate skin colonization by *Staphylococcus aureus (S. aureus*) bacteria, which is commonly seen in AD. This bacterium has been reported to increase inflammation by releasing virulence factors such as superantigens and cytotoxins.[43] Oral antibiotics are used to battle the *S. aureus* infection.[8] Another potential downside of antibiotics is that they can result in side effects such as hypersensitivity and allergic reactions.[13] Some oral systemic therapies that are accessible to treat AD are cyclosporin, methotrexate, azathioprine, and mycophenolate mofetil.[33]

Recently, mAb based treatment options have been developed to target molecules involved in the inflammatory pathway. These targeted approaches allow for greater efficacy and limit adverse side effects. Dupilumab, an anti-IL-4Rα mAb, is an FDA approved antibody treatment for AD patients. Studies for other Th2 pathway targeted mAbs, including tralokinumab and lebrikizumab are underway. Anti-IL-31 mAbs, to control pruritus, have shown benefit in the treatment of moderate-to-severe AD. Some mAbs like omalizumab, rituximab, ustekinumab, and secukinumab have had conflicting results in AD treatment; in a small study, fezakinumab, an IL-22 monoclonal antibody, showed improvement in the treatment of severe AD by altering epidermal hyperplasia. TNF-alpha inhibitors such as infliximab and etanercept have demonstrated mixed results in small clinical trials with some reports of AD exacerbation in patients taking infliximab. The topical JAK-kinase inhibitor tofacitinib improved AD in a phase II trial while the oral form, baricitinib, is still under study. Several targeted anti-pruritic agents such as tradipitant, aprepitant, serlopitant, asimdoline, and rosiglitazone are also currently being studied.[33,44]

Integrative Medicine and Future

AD, a chronic inflammatory skin disease, is an extremely challenging and complicated disorder, and heterogeneous with many underlying endotypes. It poses a substantial burden on health-care resources and on an individual's quality of life, which translates into stress, lack of sleep, itchiness, dryness, and financial loss. A common characteristic of AD includes dark patches, and dry, scaly, itchy skin, often seen as rashes on the knees, elbows, folds of the joints, backs of the hands, or on the scalp. AD is known to present itself in early childhood and initiates 'atopic march' which represents a typical sequence of atopic diseases in childhood before the development of other allergic disorders later in life. It has been seen that dermatologists have many treatment options and guidelines for AD. Still, the treatment does not seem to address AD individuals underlying issues as they vary from patient to patient.

Several patients and families with AD are seeking a more holistic approach to help address and find a cure for the disorder. As mentioned previously, there is an increased emphasis on natural therapies, and alternative medicines such as Traditional Chinese Medicine (TCM), acupuncture, and Ayurveda, in conjunction with Western medical treatments, are being pursued. Alternatively, researchers have affirmed that meditation is a practical method to manage eczema flares. Participants in the National Eczema Association (NEA)-funded study found that consistent meditation helped improve concentration and gave them a sense of control over their itch.[45]

Ayurveda-Kushtha (Skin Diseases)

In Ayurveda, the disease is described by the name "*Vicarcika*"[17,18]. *Virechana Karma,* or purgation therapy[2], followed by systemic medications are considered as the best line of management for skin disorders.[46,47] Keeping eczema flares under control can effectively have a positive impact on a patient's quality of life.

Samprapti (Pathogenesis) and Roopa (Symptoms)

Vicarcika is *Kshudra*; *Kushtha* diseases have a tendency of exacerbations.[14] The term eczema is broadly applied to an array of persistent skin rashes characterized by redness, edema, itching and dryness, with likely crusting, flaking, blistering, cracking, oozing, or bleeding.[20] According to Ayurvedic classical texts, *Vicarcika* has following symptoms: *Kandu* (excessive itching), *Pidika* (vesicle/boil/pustule), *Shyavata* (discoloration), *Bahusrava* (profuse oozing), *Lasikasrava Raji* (marked lining/lichenification), *Ruja* (Pain), *Rukshata* (excessive dryness). The main causative factor is *Agnimandhy*a, or low fire.[48] Sometimes, changes in skin discoloration can be observed, especially when lesions are healing. Eczema is usually a dry disorder with thick, scaly skin and hyperpigmentation.[49] Visible criss-cross markings and lichenification are also seen in these patients.[50]

The pathogenesis involved in the manifestation of *Vicarcika*, *and Kustha roga* in general, is vitiation of *Tridosha*, predominantly of *Kapha Dosha*. The *Sushruta Samhita* defines *Vicarcika's Roopa* as excessive pain and itchng.[18,51] Sushruta categorized *Vicarcika* (dry eczema) as *Pitta pradhan Kshudra kushtha*. The *Charak Samhita* describes *Vicarcika* as having pimples which are itchy, blackish, and with excessive discharge.[14]

Upasaya (Treatment)

Shodhana and *Shamana* therapy are the two types of treatment recommended for *Kushtha* diseases, like eczema or *Vicarcika*.[52] *Shodhana Chikitsa*, or purifying treatments, are used to eliminate the vitiated *doshas* and are considered beneficial for skin diseases. In Ayurvedic medicine, eczema is mainly treated with *Panchakarma* therapy. When a full *Shodhana chikitsa* (i.e *Panchakarma*) is not possible due to weakened *Ojas, Vicarcika* is then treated by *Shamana chikitsa*. *Shamanoushadis* or medicines are administered to help correct the dhatus.[53] Oral medicines for detoxification or purification are also used in the beginning of the treatment followed by external topical application at the end.

Charaka has mentioned that in all the chronic diseases, *Rasayana* drugs should be prescribed.[22] *Rasayanas* or rejuvenating medicines are prescribed for nourishment to the skin. *Rasayana* includes herbs like *guduchi (Tinospora cardifolia)* and *bhringaraj (Eclipta alba)*. Other herbs often used in Ayurveda to treat eczema symptom include cardamom, turmeric, *triphala, neem*, and Indian *sarsaparilla*. It is known that stress can also give rise to eczema

symptoms, Ayurvedic herbs such as *kava kava, winter cherry*, and *brahmi*, that support the nervous system can be helpful in controlling these symptoms. Yoga, massages, and meditation can help to reduce stress. An Ayurvedic treatment plan for eczema includes a diet plan, which should be rich in whole and unprocessed foods. Remedies like oatmeal bath can be beneficial. Using coconut oil for dryness is recommended, and coconut has antibacterial properties that may avert harmful, infection-causing bacteria from entering cracked skin. Treatment herbs include hempseed oil, which can hydrate and strengthen the skin while preventing bacterial infections, sunflower oil, which can reduce inflammation and increase hydration, witch hazel, which can help control inflammations, and finally aloe vera gel, which can be used to relieve inflamed skin and itching.

In a study, a patient was treated with *Guduchyadikwath*, *Arogyavardhini Vati* (internal medication) and *Triphala Churna, Vasa Churna* and *Karanja Tail* (local application) for a month and improvement in all symptoms was observed and skin became normal with no discoloration.[16] Similarly, in 2009, Mandip and Chandola[20] performed a clinical study to understand the role of *Shirishadi* decoction administered orally and simultaneously with *Snuhyadi lepa* applied topically to manage AD/eczema. The study data showed that the combination treatment resulted in a complete remission in 18.2% patients, a marked improvement was observed in 42.4% patients and a moderate improvement was seen in 36.4% patients with a high recurrence rate of 80% in these patients. The same authors in 2010,[20,47] decided to conduct another clinical study with *Rasayana* herbs such as *guduchi* and *bhringaraja*, based on Charaka's recommendation. In this study *guduchi* and *bhringaraja* were given after *Koshtha Shuddhi* with *Aragvadha (Cassia fistula) Hima* or cold infusion, and simultaneously with *Shirishadi* decoction orally and applying *Snuhyadi lepa* externally. This combination provided complete remission to 22.6% of patients with *Vicarcika* and controlled the recurrences of the disease in 89.5% of patients. The use of *Koshtha Shuddhi* decreased the recurrence of the disease.

Guduchi is *Kushthaghna Rasayana* and has proved to have antiallergic effects. It is also an antioxidant, an immunostimulant, and has hepatoprotective properties.[54] Likewise, *bhringaraja* is also *Kushthaghn Rasayana* and *Keshya* (hair). It is an antioxidant, anti-inflammatory, and has tonic actions. Based on the study data, it was concluded that the addition of *guduchi* and *bhringaraja Rasayana* to *Shirishadi* decoction and *Snuhyadi*

lepa significantly controlled the recurrence of eczema. However, no significant cure rate differences were observed between the *Rasayana* group and the no *Rasayana* group. The results of a third study showed improved cure rate when *Virechana Karma* was performed prior to the administration of *guduchi-bhringaraja Rasayana* and *Shirishadi* decoction orally and *Snuhyadi lepa* externally. The cure rate increased to 81.3% for the patients of *Vicarcika* and control in recurrences was observed.[40,20] Other treatments using *Rakta mokshna*, or leeches, have shown improvement of the symptoms of *Vicarcika*. According to Sushruta, regular bloodletting can help develop resistance against all types of skin diseases.[51,55]

Eczema affects the body and the mind. Ayurveda hopes to target this disease by improving the immune system, managing eczema related symptoms, removing the toxins, and strengthening the mind. Several alternative and Western treatment options are available to effectively manage *kushtha* or skin diseases. A strategic treatment regimen combined with lifestyle changes including stress management, yoga, massage therapy, good hygiene, and a healthy diet can result in the prevention, control, and management of eczema flare ups (or *Vicarcika*), and thus improve the patient's quality of life.

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Published online 2018 Feb 20. doi: 10.5114/ada.2018.73159
PMCID: PMC5872242
PMID: 29599666

Structure and function of the epidermal barrier in patients with atopic dermatitis – treatment options. Part one

Jagoda Pelc, Magdalena Czarnecka-Operacz, and Zygmunt Adamski

Abstract

Atopic dermatitis is a chronic, recurrent inflammatory skin disease, which is frequently familial. The main cause of the disease seems to be a defect of the epidermal barrier resulting from a genetic predisposition concerning the epidermis, functioning of the immune system as well as environmental factors (which are not related to the immune system). Genes responsible for encoding protein S100, filaggrin, proteases and their inhibitors are the main genes related to the problem of epidermal barrier dysfunction. There is a close connection between structural and immunological processes. Increased expression of cytokine Th2 profile belongs to the latter category. The objective of the present paper is to describe the influence of aforementioned factors on epidermis structure and dysfunction which leads to clinical symptoms of atopic dermatitis.

Keywords: atopic dermatitis, epidermal barrier, filaggrin, cytokines

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Int J Ayurveda Res. 2010 Oct-Dec; 1(4): 268–270.
doi: 10.4103/0974-7788.76792

A case discussion on eczema

Pallavi Hegde, D T Hemanth, S V Emmi, M P Shilpa, Pradeep S Shindhe, and Y M Santosh
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Abstract

Eczema is a form of dermatitis where inflammation of epidermis occurs. The exact cause of eczema is not known. Although it is activated by the immune system and is related to allergic reactions, it is not the same as other allergic reactions. In Ayurveda, the disease is described by the name "*Vicharchika*." *Virechana* is the best line of management for skin disorders. Controlling eczema more effectively can make a radical improvement to the patient's quality of life. A case report of 45-year-old male, who presented with complaints of rashes over dorsum of both foot associated with intense itching and burning sensation, oozing wound posterior to lateral malleolus and dorsum of left foot has been presented here.

Keywords: Eczema, *vicharchika*, *virechana*

Reference 3

The Socioeconomic Impact of Atopic Dermatitis in the United States: A Systematic Review

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https://doi.org/10.1111/j.1525-1470.2007.00572.x

Abstract: The aim of this study was to review studies examining the direct and indirect costs of atopic dermatitis in the United States. A search was performed using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the International Agency for Health Technology Assessment (INAHTA) database, and the Cochrane Library. All abstracts were reviewed for the following criteria: original cost data, studies performed in

the United States, and English language. The search yielded 418 papers. Fifty-nine papers were reviewed in detail, and four studies were found that met the inclusion criteria. These cost-identification analyses estimated the cost of atopic dermatitis heterogeneously and could not be compared directly. National cost estimates ranged widely, from $364 million to $3.8 billion US dollars per year. The cost of atopic dermatitis is significant and will likely increase in proportion to increasing disease prevalence. Measurement of the cost of atopic dermatitis in the United States has been limited to direct cost-identification analyses, with few studies measuring the indirect cost of disease.

Reference 4

Prevalence and Incidence of Atopic Dermatitis: A Systematic Review
Simon Bylund[1#], Laura B. von Kobyletzki[2–4#], Marika Svalstedt[5] and Åke Svensson[3]
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[#]These authors contributed equally.
ABSTRACT
The primary objective of this study was to systematically review and analyse epidemiological studies of the prevalence and incidence of atopic dermatitis (AD) during childhood and adulthood, focusing on data from the 21st century. A systematic search of PubMed, EMBASE and Google (manual search) was performed in June 2019, followed by data abstraction and study quality assessment (Newcastle–Ottawa Scale). Cross-sectional and longitudinal epidemiological studies of individuals with AD (doctor-diagnosed or standardized definition) were included. Of 7,207 references reviewed, 378 moderate/good-quality studies were included: 352 on prevalence of AD and 26 on incidence of AD. In the 21st century, the 1-year prevalence of doctor-diagnosed AD ranged from 1.2% in Asia to 17.1% in Europe in adults, and 0.96% to 22.6% in children in Asia. The 1-year incidence ranged from 10.2 (95% confidence interval (95% CI) 9.9–10.6) in Italy to 95.6 (95% CI 93.4–97.9) per 1,000 person-years in children in Scotland. There were few recent studies on incidence of AD in the 21st century and no studies on adults only; most studies were conducted in Europe and the USA. Epidemiological studies on childhood and adulthood AD in different continents are still needed, especially on the incidence of AD during adulthood.

Reference 5
https://nationaleczema.org/eczema/

Reference 6
Review Genetics and Epigenetics of Atopic Dermatitis: An Updated Systematic Review Maria J Martin 1,2,† , Miguel Estravís 1,2,3,† , Asunción García-Sánchez 1,2,3, , Ignacio Dávila 1,2,4 , María Isidoro-García 1,2,5,6 and Catalina Sanz 1,2,*
Genes 2020, 11, 442; doi:10.3390/genes11040442
Abstract: Background: Atopic dermatitis is a common inflammatory skin disorder that affects up to 15–20% of the population and is characterized by recurrent eczematous lesions with intense itching. As a heterogeneous disease, multiple factors have been suggested to explain the nature of atopic dermatitis (AD), and its high prevalence makes it necessary to periodically compile and update the new information available. In this systematic review,

the focus is set at the genetic and epigenetic studies carried out in the last years. Methods: A systematic literature review was conducted in three scientific publication databases (PubMed, Cochrane Library, and Scopus). The search was restricted to publications indexed from July 2016 to December 2019, and keywords related to atopic dermatitis genetics and epigenetics were used. Results: A total of 73 original papers met the inclusion criteria established, including 9 epigenetic studies. A total of 62 genes and 5 intergenic regions were described as associated with AD. Conclusion: Filaggrin (FLG) polymorphisms are confirmed as key genetic determinants for AD development, but also epigenetic regulation and other genes with functions mainly related to the immune system and extracellular matrix, reinforcing the notion of skin homeostasis breakage in AD. Keywords: atopic dermatitis; genetics; epigenetics; skin barrier; genetic association studies; DNA methylation; omics

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Nature. Author manuscript; available in PMC 2013 Feb 15.
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Nature. 2008 Jul 24; 454(7203): 445–454.
doi: 10.1038/nature07204

The development of allergic inflammation

Stephen J. Galli,[1,2] Mindy Tsai,[1] and Adrian M. Piliponsky[1]

Abstract

Allergic disorders, such as anaphylaxis, hay fever, eczema and asthma, now afflict roughly 25% of people in the developed world. In allergic subjects, persistent or repetitive exposure to allergens, which typically are intrinsically innocuous substances common in the environment, results in chronic allergic inflammation. This in turn produces long-term changes in the structure of the affected organs and substantial abnormalities in their function. It is therefore important to understand the characteristics and consequences of acute and chronic allergic inflammation, and in particular to explore how mast cells can contribute to several features of this maladaptive pattern of immunological reactivity.

Reference 8

Eczema

Valerie Nemeth; Justin Evans.
Last Update: November 20, 2020.

Continuing Education Activity

Eczema, also known as atopic dermatitis, is a common chronic skin condition that can lead to recurrent infections and poor quality of life if left untreated. This activity reviews the evaluation and management of eczema and highlights the role of interprofessional teams in improving outcomes for patients with this condition.

Objectives:

- Review the pathophysiology of eczema.
- Outline the adverse effects of poorly controlled eczema.
- Summarize the treatment options for eczema.
- Describe the importance of improving care coordination amongst the interprofessional team to improve outcomes for patients with eczema.

Reference 9

Indian J Dermatol. 2016 Nov-Dec; 61(6): 649–655.
doi: 10.4103/0019-5154.193674
PMCID: PMC5122281

PMID: 27904184

Current Understanding in Pathogenesis of Atopic Dermatitis

Tess McPherson

Abstract

There have been advances in our understanding of the complex pathogenesis of atopic eczema over the past few decades. This article examines the multiple factors which are implicated in this process.

Keywords: *Atopic dermatitis*, *atopic march*, *filaggrin*

Reference 10

F1000 Med Rep. 2011; 3: 2.

Published online 2011 Jan 14. doi: 10.3410/M3-2

The allergy gene: how a mutation in a skin protein revealed a link between eczema and asthma

W. H. Irwin McLean

Abstract

Ichthyosis vulgaris is a common genetic skin disorder characterized by dry, scaly skin. About 1% of the European population have the full presentation of ichthyosis vulgaris; up to 10% have a milder, subclinical form. Atopic eczema is the most common, inflammatory skin condition, affecting 20% of children. It is often accompanied by a number of other allergies, including atopic asthma. Atopic eczema is a complex trait, where predisposing genes in combination with environmental stimuli produce the disease. Recently, we reported the first loss-of-function genetic mutations in the filaggrin gene as the cause of ichthyosis vulgaris. We noted people with ichthyosis vulgaris also have atopic eczema (and vice versa) and that the filaggrin gene sits in a known atopic eczema susceptibility locus. We went on to confirm that filaggrin mutations, carried by up to 10% of the population, are the major genetic predisposing factor for atopic eczema and the various allergies associated with atopic eczema. Filaggrin is a highly abundant protein expressed in the uppermost part of the epidermis that is critical to the formation and hydration of the stratum corneum—the outermost dead cell layers responsible for the barrier function of the skin. Filaggrin deficiency leads to a "leaky" skin barrier that allows higher than normal water loss (explaining the dry, scaly skin), as well as allowing entry of allergens through the epidermis where they trigger inflammatory and allergic immune responses (atopic eczema and allergies). This work has placed the skin barrier at the center stage of eczema and allergy research and has kick-started new therapy development programs aimed at repairing or enhancing skin-barrier function as a means of treating or preventing these very common diseases.

Reference 11

Molecular Genetic of Atopic dermatitis: An Update

Hani A. Al-Shobaili,(1) Ahmed A. Ahmed,(2) Naief Alnomair,(3) Zeiad Abdulaziz Alobead,(4) and Zafar Rasheed(5

Abstract

Atopic dermatitis (AD) is a chronic multifactorial inflammatory skin disease. The pathogenesis of AD remains unclear, but the disease results from dysfunctions of skin barrier and immune response, where both genetic and environmental factors play a key role. Recent studies demonstrate the substantial evidences that show a strong genetic association with AD. As for example, AD patients have a positive family history and have a concordance rate in twins. Moreover, several candidate genes have now been suspected that play a central role in the genetic background of AD. In last decade advanced

procedures similar to genome-wide association (GWA) and single nucleotide polymorphism (SNP) have been applied on different population and now it has been clarified that AD is significantly associated with genes of innate/adaptive immune systems, human leukocyte antigens (HLA), cytokines, chemokines, drug-metabolizing genes or various other genes. In this review, we will highlight the recent advancements in the molecular genetics of AD, especially on possible functional relevance of genetic variants discovered to date.
Keywords: Atopic dermatitis, molecular genetics, immune genes, cytokine, chemokine, drug-metabolizing genes

Reference 12

Review Article

Atopic dermatitis: the skin barrier and beyond

T. Tsakok
R. Woolf
C.H. Smith
S. Weidinger
C. Flohr

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Funding sources None.
Conflicts of interest S.W. has performed consultancy for Sanofi-Genzyme, Astellas and Novartis; has received independent research grants from Novartis, Biogen and Pfizer; and is involved in performing clinical trials with many pharmaceutical companies manufacturing drugs used for the treatment of conditions including psoriasis and atopic dermatitis. C.H.S. has departmental funding from pharmaceutical companies involved in manufacturing therapies for atopic dermatitis, including Roche, Regeneron and Novartis. C.F. has advised Sanofi on their conventional systemic therapy registry EUROSTAD and Roche/Genentech on the design of a biologics trial.
T.T. and R.W. contributed equally to this review.

Reference 13

Atopic Dermatitis: An Overview - American Family Physician." 1 Jul. 2012, https://www.aafp.org/afp/2012/0701/p35.html.

REBECCA BERKE, MD; ARSHDEEP SINGH, MD; and MARK GURALNICK, MD, Kaiser Permanente's Woodland Hills Family Medicine Residency Program, Woodland Hills, California

Am Fam Physician. 2012 Jul 1;86(1):35-42.

▶ Patient information: See related handout on eczema, written by the authors of this article.

Atopic dermatitis, also known as atopic eczema, is a chronic pruritic skin condition affecting approximately 17.8 million persons in the United States. It can lead to significant morbidity. A simplified version of the U.K. Working Party's Diagnostic Criteria can help make the diagnosis. Asking about the presence and frequency of symptoms can allow physicians to grade the severity of the disease and response to treatment. Management consists of relieving symptoms and lengthening time between flare-ups. Regular, liberal use of emollients is recommended. The primary pharmacologic treatment is topical corticosteroids. Twice-daily or more frequent application has not been shown to be more effective than once-daily application. A maintenance regimen of topical corticosteroids may reduce relapse rates in patients who have recurrent moderate to severe atopic dermatitis. Pimecrolimus and tacrolimus are calcineurin inhibitors that are recommended as second-line treatment for persons with moderate to severe atopic dermatitis and who are at risk of

atrophy from topical corticosteroids. Although the U.S. Food and Drug Administration has issued a boxed warning about a possible link between these medications and skin malignancies and lymphoma, studies have not demonstrated a clear link. Topical and oral antibiotics may be used to treat secondary bacterial infections, but are not effective in preventing atopic dermatitis flare-ups. The effectiveness of alternative therapies, such as Chinese herbal preparations, homeopathy, hypnotherapy/biofeedback, and massage therapy, has not been established.

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P. V. Sharma. Charaka Samhita. Chapter VII. Page 127-130. https://archive.org/details/CharakaSamhitaTextWithEnglishTanslationP.V.Sharma/page/n157/mode/2up. Chapter VII. (21-26)

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https://www.carakasamhitaonline.com/index.php?title=Kushtha_Chikitsa#11.Vic.C4.81rcik.C4.81_ku.E1.B9.A3.E1.B9.ADha

Reference 16
International Journal of Herbal Medicine 2017; 5(2): 38-40
Effect of Shamana chikitsa in Vicharchika (wsr. Chronic Eczema): A case study
Bharat Mungara and Shreeba Jadeja Anita Desai
Abstract
Dermatitis, commonly known as eczema, is a common chronic, relapsing skin disease characterized by pruritus, disrupted epidermal barrier function, and immunoglobulin E-mediated sensitization to food and environmental allergens. Atopic dermatitis is a complex disease that arises from interactions between genes and the environment. Eczema can be co-related with Vicharchika. Vicharchika can be treated with Shodhana Chikitsa and Shamana Chikitsa. Here, a female subject, aged 17 years, Student, living presently in Ahmedabad, with the chief complains of kandu (itching) on affected sites. The other associated symptoms were Burning, Fissure and scaling since 6 month. Patient first took allopathy medication but didn't get benefited then she wanted to take Ayurvedic medication. After 1month of treatment with Guduchyadikwath, Arogyavardhini Vati (internal medication) and Triphala Churna, Vasa Churna and Karanja Tail (local application) all symptoms improved and skin became normal and no discoloration. Keywords: Eczema, Dermatitis, Shamana Chikitsa, Vicharchika, Arogyavardhini Vati, Guduchyadi Kwatha

Reference 17
Charak Samhita Research, Training and Skill Development Centre (CSRTSDC). Chapter 7. Management of Kushtha (Skin Diseases). Kushtha Chikitsa-Chikitsa Sthana- 4.1.146.Vichārchikā
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https://www.carakasamhitaonline.com/index.php?title=Kushtha_Chikitsa#Dosha_dominance_in_types_of_kushtha

Reference 20
Role of *Rasayana* in Cure and Prevention of Recurrence of *Vicharchika* (Eczema)
Mandip Kaur* and H. M. Chandola**
2010;31(1):33-39. doi:10.4103/0974-8520.68207

Abstract
Generally, skin diseases run a chronic course and the recurrence is very common. Mandip and Chandola (2009) reported that *Shirishadi* Decoction administered orally and simultaneously *Snuhyadi Lepa* applied externally to the patients of *Vicharchika* (Eczema) provided complete remission to 18.2% patients, marked improvement to 42.4% patients and moderate improvement to 36.4% patients but the recurrence rate was very high i.e. 80%. *Charaka*, in the context of the treatment of *Apasmara* mentions that in all the chronic diseases, *Rasayana* drugs should be prescribed. As eczema is a chronic disease and its recurrences are very common, therefore, it was thought desirable to evaluate the role of the *Rasayana* drugs in the cure and prevention of the recurrence of *Vicharchika* (Eczema). In this study, total 38 patients of *Vicharchika* (Eczema) were registered, among which 31 patients completed the full course of treatment. These patients were first subjected to *Koshtha Shuddhi* done with *Aragvadha (Cassia fistula) Hima* administered orally at bedtime for initial eight days. Thereafter 30 ml of *Shirishadi* Decoction and 6 gm of *Guduchi (Tinospora cardifolia)* and *Bhringaraja (Eclipta alba)* powder was given with *Ghrita*. Both the drugs were given twice daily after meals orally. Simultaneously, *Snuhyadi Lepa* was applied on the eczematous lesions. Results of the study showed that addition of Rasayana drugs provided complete remission to 22.6% and checked the recurrence of the disease in the 89.5% patients of *Vicharchika* (Eczema).
Keywords: *Vicharchika*, *Rasayana*, *Koshtha Shuddhi*, *Shirishadi* Decoction, *Snuhyadi Lepa*, *Guduchi- Bhringaraja Rasayana*, Eczema, Recurrence

Reference 21
Charak Samhita Research, Training and Skill Development Centre (CSRTSDC). Nidana Sthana Chapter 5. Diagnosis and etiopathogenesis of Skin diseases
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Reference 22
Charak Samhita Research, Training and Skill Development Centre (CSRTSDC). Chikitsa Sthana Chapter 1. Rejuvenation therapy. 2.1.5Benefits of *Rasayana*
https://www.carakasamhitaonline.com/index.php?title=Rasayana_Adhyaya#Benefits_of_Rasayana

Reference 23
Severe Atopic Dermatitis Often Puts a Dent in Quality of Life - Medscape - Mar 04, 2021.

Reference 24
https://www.niams.nih.gov/health-topics/atopic-dermatitis

Reference 25
https://nationaleczema.org/eczema/types-of-eczema/contact-dermatitis/

Reference 26
Scratching Induces Overactivity in Motor-Related Regions and Reward System in Chronic Itch Patients
Hideki Mochizuki [1], Alexandru D P Papoiu [2], Leigh A Nattkemper [1], Andrew C Lin [1], Robert A Kraft [3], Robert C Coghill [4], Gil Yosipovitch [5]
Abstract
Scratching evokes a rewarding and pleasurable sensation, particularly in chronic itch patients. To date, no study has investigated the cerebral activity during scratching in chronic itch patients and whether it differs from that in healthy subjects. Using arterial spin labeling functional magnetic resonance imaging, we analyzed and compared the cerebral mechanism of self-scratching and its correlation with pleasurability in 10 patients with chronic itch and in 10 healthy controls. Cowhage was applied to the right forearm to induce itch. Scratching significantly attenuated the itch sensation ($P<0.001$) and evoked an associated pleasurability. Scratching-induced pleasurability significantly activated the reward system in the chronic itch and healthy groups, confirming that this reward system has a crucial role in scratching-induced pleasurability. A higher activity during scratching in chronic itch patients, versus healthy controls, was noted in brain regions related to motor control and motivation to act, including the supplementary motor area, premotor cortex, primary motor cortex, and midcingulate cortex, as well as the caudate nucleus involved in the reward system. This overactivity may be associated with the addictive scratching and/or neural hypersensitization.

Reference 27
Source: https://nationaleczema.org/eczema/types-of-eczema/

Reference 28
Atopic Dermatitis
Atopic Dermatitis: Global Epidemiology and Risk Factors
Nutten S
Ann Nutr Metab 2015;66(suppl 1):8-16
https://doi.org/10.1159/000370220
Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease posing a significant burden on health-care resources and patients' quality of life. It is a complex disease with a wide spectrum of clinical presentations and combinations of symptoms. AD affects up to 20% of children and up to 3% of adults; recent data show that its prevalence is still increasing, especially in low-income countries. First manifestations of AD usually appear early in life and often precede other allergic diseases such as asthma or allergic rhinitis. Individuals affected by AD usually have genetically determined risk factors affecting the skin barrier function or the immune system. However, genetic mutations alone might not be enough to cause clinical manifestations of AD, and it is merely the interaction of a dysfunctional epidermal barrier in genetically predisposed individuals with harmful effects of environmental agents which leads to the development of the disease. AD has been described as an allergic skin disease, but today, the contribution of allergic reactions to the initiation of AD is challenged, and it is

proposed that allergy is rather a consequence of AD in subjects with a concomitant underlying atopic constitution. Treatment at best achieves symptom control rather than cure; there is thus a strong need to identify alternatives for disease prevention.

Reference 29

J Invest Dermatol

2008 Nov;128(11):2625-2630.

Possible pathogenic role of Th17 cells for atopic dermatitis

Chizuko Koga [1], Kenji Kabashima [2], Noriko Shiraishi [3], Miwa Kobayashi [3], Yoshiki Tokura [3]

Abstract

The critical role of IL-17 has recently been reported in a variety of conditions. Since IL-17 deeply participates in the pathogenesis of psoriasis and keratinocyte production of certain cytokines, the involvement of T helper cell 17 (Th17) in atopic dermatitis (AD) is an issue to be elucidated. To evaluate the participation of Th17 cells in AD, we successfully detected circulating lymphocytes intracellularly positive for IL-17 by flow cytometry, and the IL-17+ cell population was found exclusively in CD3+CD4+ T cells. The percentage of Th17 cells was increased in peripheral blood of AD patients and associated with severity of AD. There was a significant correlation between the percentages of IL-17+ and IFN-gamma+ cells, although percentage of Th17 cells was not closely related to Th1/Th2 balance. Immunohistochemically, IL-17+ cells infiltrated in the papillary dermis of atopic eczema more markedly in the acute than chronic lesions. Finally, IL-17 stimulated keratinocytes to produce GM-CSF, TNF-alpha, IL-8, CXCL10, and VEGF. A marked synergistic effect between IL-17 and IL-22 was observed on IL-8 production. The number of Th17 cells is increased in the peripheral blood and acute lesional skin of AD. Th17 cells may exaggerate atopic eczema.

Reference 30

https://emedicine.medscape.com/article/1049085-overview#a5

Reference 31

J Allergy Clin Immunol
2014 Feb;133(2):448-60.

A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: Involvement of TRPV1 and TRPA1

Ferda Cevikbas [1], Xidao Wang [2], Tasuku Akiyama [3], Cordula Kempkes [4], Terhi Savinko [5], Attila Antal [6], Gabriela Kukova [6], Timo Buhl [4], Akihiko Ikoma [4], Joerg Buddenkotte [7], Vassili Soumelis [8], Micha Feld [6], Harri Alenius [5], Stacey R Dillon [9], Earl Carstens [3], Bernhard Homey [10], Allan Basbaum [11], Martin Steinhoff [12]

Abstract

Background: Although the cytokine IL-31 has been implicated in inflammatory and lymphoma-associated itch, the cellular basis for its pruritic action is yet unclear.
Objective: We sought to determine whether immune cell-derived IL-31 directly stimulates sensory neurons and to identify the molecular basis of IL-31-induced itch.
Methods: We used immunohistochemistry and quantitative real-time PCR to determine IL-31 expression levels in mice and human subjects. Immunohistochemistry, immunofluorescence, quantitative real-time PCR, in vivo pharmacology, Western blotting,

single-cell calcium imaging, and electrophysiology were used to examine the distribution, functionality, and cellular basis of the neuronal IL-31 receptor α in mice and human subjects.
Results: Among all immune and resident skin cells examined, IL-31 was predominantly produced by TH2 and, to a significantly lesser extent, mature dendritic cells. Cutaneous and intrathecal injections of IL-31 evoked intense itch, and its concentrations increased significantly in murine atopy-like dermatitis skin. Both human and mouse dorsal root ganglia neurons express IL-31RA, largely in neurons that coexpress transient receptor potential cation channel vanilloid subtype 1 (TRPV1). IL-31-induced itch was significantly reduced in TRPV1-deficient and transient receptor channel potential cation channel ankyrin subtype 1 (TRPA1)-deficient mice but not in c-kit or proteinase-activated receptor 2 mice. In cultured primary sensory neurons IL-31 triggered Ca(2+) release and extracellular signal-regulated kinase 1/2 phosphorylation, inhibition of which blocked IL-31 signaling in vitro and reduced IL-31-induced scratching in vivo.
Conclusion: IL-31RA is a functional receptor expressed by a small subpopulation of IL-31RA(+)/TRPV1(+)/TRPA1(+) neurons and is a critical neuroimmune link between TH2 cells and sensory nerves for the generation of T cell-mediated itch. Thus targeting neuronal IL-31RA might be effective in the management of TH2-mediated itch, including atopic dermatitis and cutaneous T-cell lymphoma.
Keywords: AD; AITC; Allyl isothiocyanate; Atopic dermatitis; Cytokine; DRG; Dorsal root ganglia; ERK; Extracellular signal-regulated kinase; GRPR; Gastrin-releasing peptide receptor; HBSS; Hanks balanced salt solution; High-power field; IB4; Isolectin B4; KO; Knockout; MEK; Mas-related G protein–coupled receptor; Mitogen-activated protein kinase enzyme; Mrgpr; NPR-A; Natriuretic peptide receptor A; OSMRβ; OVA; Oncostatin M receptor β; Ovalbumin; PAR-2; Proteinase-activated receptor 2; Quantitative real-time PCR; SC; SEB; Spinal cord; Staphylococcal enterotoxin B; TG; TRPA1; TRPV1; Transient receptor channel potential cation channel ankyrin subtype 1; Transient receptor potential cation channel vanilloid subtype 1; Trigeminal ganglion; atopic dermatitis; hpf; qPCR; sensory nerve; skin; transient receptor potential channel.

Reference 32

Cell
2017 Sep 21;171(1):217-228.e13.
doi: 10.1016/j.cell.2017.08.006. Epub 2017 Sep 7.

Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch

Landon K Oetjen [1], Madison R Mack [1], Jing Feng [2], Timothy M Whelan [1], Haixia Niu [1], Changxiong J Guo [2], Sisi Chen [3], Anna M Trier [1], Amy Z Xu [1], Shivani V Tripathi [1], Jialie Luo [2], Xiaofei Gao [2], Lihua Yang [4], Samantha L Hamilton [4], Peter L Wang [5], Jonathan R Brestoff [5], M Laurin Council [6], Richard Brasington [7], András Schaffer [8], Frank Brombacher [9], Chyi-Song Hsieh [10], Robert W Gereau 4th [11], Mark J Miller [4], Zhou-Feng Chen [2], Hongzhen Hu [2], Steve Davidson [3], Qin Liu [2], Brian S Kim [12]

Abstract

Mammals have evolved neurophysiologic reflexes, such as coughing and scratching, to expel invading pathogens and noxious environmental stimuli. It is well established that these responses are also associated with chronic inflammatory diseases, including asthma and atopic dermatitis. However, the mechanisms by which inflammatory pathways promote sensations such as itch remain poorly understood. Here, we show that type 2 cytokines directly activate sensory neurons in both mice and humans. Further, we demonstrate that chronic itch is dependent on neuronal IL-4Rα and JAK1 signaling. We also observe that patients with recalcitrant chronic itch that failed other immunosuppressive therapies

markedly improve when treated with JAK inhibitors. Thus, signaling mechanisms previously ascribed to the immune system may represent novel therapeutic targets within the nervous system. Collectively, this study reveals an evolutionarily conserved paradigm in which the sensory nervous system employs classical immune signaling pathways to influence mammalian behavior.
Keywords: IL-13; IL-4; IL-4Rα; JAK1; atopic dermatitis; itch; pruriceptor; pruritus; type 2 cytokines.

Reference 33

J Clin Aesthet Dermatol. 2019 Feb; 12(2): 39–41.

MONOCLONAL ANTIBODY THERAPIES for Atopic Dermatitis: Where Are We Now in the Spectrum of Disease Management?

James Q. Del Rosso, DO

Abstract

Atopic dermatitis (AD) is a chronic disorder that requires thorough patient education and a therapeutic management strategy designed to control flares, decrease recurrences, and reduce pruritus. In cases that cannot be controlled by proper skin care and barrier repair, topical therapy, and avoidance of triggers, systemic therapy is often required to control flares and maintain remission. It is important for clinicians to avoid becoming overly dependent on the intermittent use of systemic corticosteroid therapy to control flares, without incorporating other treatment options that might more optimally control AD over time. This article provides an overview of systemic therapies, including conventional oral therapy options and injectable biologic agents, that modulate the immune dysregulation in AD. Major emphasis is placed on the monoclonal antibodies currently available (e.g., dupilumab) for the treatment of AD, as well as those in latter stages of development, with a focus on agents targeting IL-4and/or IL-13.

Keywords: Atopic dermatitis, calcineurin inhibitors, phosphodiesterase-4 inhibitors, immunosuppressants, interleukin-4, interleukin-13

Reference 34

Review
Allergol Int
2011 Mar;60(1):1-9.
doi: 10.2332/allergolint.10-RAI-0270. Epub 2011 Dec 25.

Filaggrin gene defects and the risk of developing allergic disorders

Rinko Osawa [1], Masashi Akiyama, Hiroshi Shimizu

Abstract

Filaggrin is a key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier. Mutations in the gene encoding filaggrin (FLG) have been identified as the cause of ichthyosis vulgaris (IV) and have been shown to be major predisposing factors for atopic dermatitis (AD). Approximately 40 loss-of-function FLG mutations have been identified in patients with ichthyosis vulgaris (IV) and/or atopic dermatitis (AD) in Europe and Asia. Major differences exist in the spectra of FLG mutations observed between different ancestral groups. Notably, prevalent FLG mutations are distinct between European and Asian populations. Many cohort studies on FLG mutations in AD have revealed that approximately 25-50% of AD patients harbour filaggrin mutations as a predisposing factor. In addition, FLG mutations are significantly associated with AD-associated asthma. The risk for developing allergic rhinitis is also significantly higher with a FLG mutation, both with and without accompanying AD. Recent studies have hypothesized

that skin barrier defects caused by FLG mutations allows allergens to penetrate the epidermis and to interact with antigen-presenting cells, leading to the development of atopic disorders including asthma. The restoration of skin barrier function seems a feasible and promising strategy for prophylactic treatment of AD patients with FLG mutations.

Reference 35

Ann Allergy Asthma Immunol
2020 Jan;124(1):36-43.
doi: 10.1016/j.anai.2019.10.008. Epub 2019 Oct 14.

The role of filaggrin in atopic dermatitis and allergic disease

Catherine Drislane [1], Alan D Irvine [2]

Abstract

Objective: To provide an overview of filaggrin biology and the role of filaggrin variants in atopic dermatitis (AD) and allergic disease.

Data sources: We performed a PubMed literature review consisting mainly of studies relating to filaggrin in the last 5 years.

Study selections: We selected articles that were found in PubMed using the search terms filaggrin, atopic dermatitis, skin barrier, and atopy.

Results: Filaggrin plays an important role in the development of AD and allergic disease. Novel methods in measuring filaggrin expression and identifying filaggrin mutations aid in stratifying this patient cohort. We review new insights into understanding the role of filaggrin in AD and allergic disease.

Conclusion: Filaggrin remains a very important player in the pathogenesis of atopic dermatitis and allergic disease. This review looks at recent studies that aid our understanding of this crucial epidermal protein.

Reference 36

An Bras Dermatol. 2016 Jul-Aug; 91(4): 472–478.
doi: 10.1590/abd1806-4841.20164412
PMCID: PMC4999106

Skin barrier in atopic dermatitis: beyond filaggrin*

Mariana Colombini Zaniboni,[1] Luciana Paula Samorano,[1] Raquel Leão Orfali,[1] and Valéria Aoki

Abstract

Atopic dermatitis is a chronic inflammatory skin disease with a complex pathogenesis, where changes in skin barrier and imbalance of the immune system are relevant factors. The skin forms a mechanic and immune barrier, regulating water loss from the internal to the external environment, and protecting the individual from external aggressions, such as microorganisms, ultraviolet radiation and physical trauma. Main components of the skin barrier are located in the outer layers of the epidermis (such as filaggrin), the proteins that form the tight junction (TJ) and components of the innate immune system. Recent data involving skin barrier reveal new information regarding its structure and its role in the mechanic-immunological defense; atopic dermatitis (AD) is an example of a disease related to dysfunctions associated with this complex.

Keywords: Antimicrobial cationic peptides, Claudins, Dermatitis, atopic, Immunity, innate

Reference 37

Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet* 2015;47:1449–56.

Reference 38

Liang Y, Chang C, Lu Q. The genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms. *Clin Rev Allergy Immunol* 2016;51:315–28.

Reference 39

Barnes KC: An update on the genetics of atopic dermatitis: scratching the surface in 2009. J Allergy Clin Immunol 2010;125:16-29.

Abstract

A genetic basis for atopic dermatitis (AD) has long been recognized. Historic documents allude to family history of disease as a risk factor. Before characterization of the human genome, heritability studies combined with family-based linkage studies supported the definition of AD as a complex trait in that interactions between genes and environmental factors and the interplay between multiple genes contribute to disease manifestation. A summary of more than 100 published reports on genetic association studies through mid-2009 implicates 81 genes, in 46 of which at least 1 positive association with AD has been demonstrated. Of these, the gene encoding filaggrin (FLG) has been most consistently replicated. Most candidate gene studies to date have focused on adaptive and innate immune response genes, but there is increasing interest in skin barrier dysfunction genes. This review examines the methods that have been used to identify susceptibility genes for AD and how the underlying pathology of this disease has been used to select candidate genes. Current challenges and the potential effect of new technologies are discussed.

Reference 40

Boorgula, M.P., Taub, M.A., Rafaels, N. *et al.* Replicated methylation changes associated with eczema herpeticum and allergic response. *Clin Epigenet* 11, 122 (2019). https://doi.org/10.1186/s13148-019-0714-1

Abstract

Background

Although epigenetic mechanisms are important risk factors for allergic disease, few studies have evaluated DNA methylation differences associated with atopic dermatitis (AD), and none has focused on AD with eczema herpeticum (ADEH+). We will determine how methylation varies in AD individuals with/without EH and associated traits. We modeled differences in genome-wide DNA methylation in whole blood cells from 90 ADEH+, 83 ADEH−, and 84 non-atopic, healthy control subjects, replicating in 36 ADEH+, 53 ADEH−, and 55 non-atopic healthy control subjects. We adjusted for cell-type composition in our models and used genome-wide and candidate-gene approaches.

Results

We replicated one CpG which was significantly differentially methylated by severity, with suggestive replication at four others showing differential methylation by phenotype or severity. Not adjusting for eosinophil content, we identified 490 significantly differentially methylated CpGs (ADEH+ vs healthy controls, genome-wide). Many of these associated with severity measures, especially eosinophil count (431/490 sites).

Conclusions

We identified a CpG in *IL4* associated with serum tIgE levels, supporting a role for Th2 immune mediating mechanisms in AD. Changes in eosinophil level, a measure of disease

severity, are associated with methylation changes, providing a potential mechanism for phenotypic changes in immune response-related traits.

Reference 41

BMJ. 2003 Oct 25; 327(7421): 942–943.

Topical corticosteroids in atopic dermatitis

Recent research reassures that they are safe and effective in the medium term

David J Atherton

Reference 42

"Histamine and antihistamines in atopic dermatitis - PubMed." https://pubmed.ncbi.nlm.nih.gov/21618889/. Accessed 6 Jan. 2021.

Reference 43

"Staphylococcus aureus: an underestimated factor in the ...." 22 Feb. 2019, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6409874/. Accessed 6 Jan. 2021.

Reference 44

Review

Expert Rev Clin Immunol

2019 Mar;15(3):275-288.

doi: 10.1080/1744666X.2019.1560267. Epub 2019 Jan 14.

Atopic dermatitis: a review of evolving targeted therapies

Kadra Kalamaha [1], Erin Reis [1], Shauna Newton [1], Conor Roche [1], Janet Julson [1], Hermina Fernandes [1 2], Jonathan Rodrigues [1 3 4]

Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin condition, affecting a significant number of patients of all ages. As we learn more about the pathogenesis of AD, new targeted treatment options are being developed to better tailor its management. Currently, a variety of biologic agents are utilized to target specific components and regulators of the inflammatory pathways in allergic and inflammatory conditions. These targeted therapies allow for greater efficacy while limiting adverse effects. Areas covered: This review examines the current literature in respect to several different monoclonal antibodies that are being studied toward a personalized approach in the treatment of AD. Expert opinion: Several trials examining the use of biologics for AD have demonstrated mixed success. While some have shown promise for improvement of clinical symptoms, there are several barriers to support consistent use including cost, adverse effects, small sample sizes, conflicting evidence, and lack of demonstrated long-term safety and efficacy. The ultimate goal for future research is to develop biomarkers for different AD phenotypes in order to allow for targeted therapy of AD.

Keywords: Atopic dermatitis; biologics; cytokines; eczema; immunomodulators; interleukin; monoclonal antibodies.

Reference 45

https://nationaleczema.org/meditation-ease-itch/

Reference 46

Gameti, *Rahul, Kori, V., Patel, K. S., & Rajagopalas, S. (2016). AYURVEDIC MANAGEMENT OF PSORIASIS - A CASE STUDY. International Journal of Ayurveda and Pharma Research, 4(11). Retrieved from https://ijapr.in/index.php/ijapr/article/view/502

Abstract
In Ayurveda, all types of skin diseases are described under one umbrella term of Kushtha. Acharyas have described that all Kushthas have Tridosha involvement but the type of Kushtha depends on the predominance of particular Doshas. Eka Kushtha is compared with psoriasis due to its maximum resemblance. Psoriasis is a long-lasting autoimmune disease characterized by patches of abnormal skin. These skin patches are typically red, itchy, and scaly. They may vary in severity from small and localized to extensive, large and spread in complete body. It typically presents with red patches and white scales on the top. Areas of the body most commonly affected are the back of the forearms, shins, around the navel, and the scalp. Psoriasis is generally thought to be a genetic disease which is triggered by environmental factors. Other factors such as local trauma, general illness and stress are also involved. In modern medicine, the cure of this disease is out of question as the cause is unknown. Ayurveda propounds a holistic treatment approach for psoriasis. As per Ayurvedic view point Vata, Pitta and Kapha vitiation are the major contributing pathological factors in the body. The line of treatment of skin diseases are Shodhana and Shamana therapy. Virechana Karma (purgation therapy) followed by internal medications are considered as the best line of management for skin disorders. A case report of 13 year old male child presented with well demarcated raised red scaling silvery patches on trunk and back region, limbs with itching and burning will be presented in the full paper.

Reference 47

Kaur M, Chandola H. Role of Virechana Karma in cure and prevention of recurrence of Vicharchika (Eczema). *Ayu*. 2012;33(4):505-510. doi:10.4103/0974-8520.110526

Abstract
Mandip and Chandola reported that administration of *Rasayana* (*Guduchi* and *Bhringaraja*) after *Koshtha Shuddhi* with *Aragvadha Hima* and simultaneous giving of *Shirishadi* decoction orally and applying of *Snuhyadi Lepa* externally provided complete remission to 22.6% patients of *Vicharchika* (Eczema) and checked the recurrences of the disease in the 89.5% patients. As in this group, cure rate was not up to the expectation; therefore, it was thought desirable to see whether performing of *Virechana Karma* instead of *Koshtha Shuddhi* prior to the administration of the above drugs enhances the cure rate for the *Vicharchika* (Eczema) patients. For the present study, 39 patients of *Vicharchika* (Eczema) were registered, of which 32 patients completed the full course of the treatment. These patients were given *Virechana* after preparing with the proper internal *Snehana, Abhyanga*, and *Svedana* as per classical method. After the *Samsarjana Krama*, they were administered the *Shirishadi* decoction and *Guduchi-Bhringraja Rasayana* powder orally with simultaneous local application of *Snuhyadi Lepa* on the eczematous lesions. The results of this study showed that when *Virechana Karma* was performed prior to the administration of *Guduchi-Bhringaraja Rasayana* and *Shirishadi* decoction orally and *SnuhyadiLepa* externally, it not only increased the cure rate to 81.3% in the patients of *Vicharchika* (Eczema) but also checked the recurrences to great extent as only negligible number of the patients reported the recurrence.
Keywords: Eczema, *Koshtha Shuddhi*, *Rasayana*, *Vicharchika*, *Virechana Karma*

Reference 48

Vagbhatta, Ashtang Hridaya with Sarvangasundari commentary of Arunadatta & Ayurveda Rasayana of Hemadri edited by Pt. Hari Sadashiva Shashtri, Chaukhambha Surbharati Prakashan, Varanasi,reprint 2007; Nidana Sthana 12/1, Pg.513.

Reference 49
Kaviraj Kunja Lal Bhishagratna. An English translation of the Sushruta samhita, based on original Sanskrit text. Nidana Sthanam; 1865. Chapter XIII, pages 88- 89. https://archive.org/details/englishtranslati00susruoft/page/88/mode/2up?q=247.

Reference 50
Kasper: Harrison's Principles of Internal Medicine. 16th edition. Mc Graw Hill Medical Publishing Divison: New Delhi; 2004. p. 289

Reference 51
Neelam, *Arya, Anita, S., V. K., G., & Rohit Kumar, K. (2016). AYURVEDIC MANAGEMENT OF ECZEMA (VICHARCHIKA) - A REVIEW. International Journal of Ayurveda and Pharma Research, 4(4).
https://ijapr.in/index.php/ijapr/article/view/334
Abstract
In the Ayurvedic text all skin diseases were included under the Kushtarog. Which is classified in two divisions i.e. Mahakushta and Kshudrakushta. Vicharchika is described under Kshudrakushta. The clinical presentation of Vicharchika similar to Eczema in modern dermatology. Eczema (also called atopic dermatitis) is characterized by dry itchy skin with areas of poorly demarcated erythema and scale. In the acute phase eczema may be vesicular and oozing, in the chronic phase it may become hyperpigmented and lichenified (thickened). Excoriations (scratch marks) are frequently seen. The modern science has greatly advanced, particularly in dermatology but there is no specific medicaments for sure cure of eczema but symptomatic treatments like steroids are used, but they produce serious side effects like nephrotoxicity, osteoporosis, skin cancer etc. Modern pharmacology whole body. It brings a balance of body, mind and spirit. Ayurveda believes that All Dosha in balance is essential for well-being. offers treatment for the symptom of eczema. However, it does not provide treatment for the root. Therefore, recurrence is very common. Ayurveda offers treatment for the root of eczema by cleansing vitiated Dosha and balancing the Dosha and Dhatus.

Reference 52
Kaviraj Kunja Lal Bhishagratna. An English translation of the Sushruta samhita, based on original Sanskrit text. Chikitsa Sthanam; 1865. Chapter IX.
https://archive.org/details/englishtranslati00susruoft/page/346/mode/2up?q=247

Reference 53
Savalagimath Mahesh P, Rani Jyoti, Patil Santosh F. Ayurvedic management of vicharchika with special reference to eczema: A case report. 2018, Volume: 11 (1): 92-96

Reference 54
Data Base on Medicinal Plants used in Ayurveda. 1st edition. III. New Delhi: CCRAS; 2001. Anonymous; p. 257.

Reference 55
Sushruta, SushrutaSamhita with Nibandhasangraha of dalhanacharyaandNyayachandrikaPanchika of Gayadasa.Yadava T. Shareera Sthana.7 Varanasi:ChaukhambhaSurabharatiPrakashana; 2004..383, 379p