Year-in-Review

Atopic dermatitis (updates on the itch)

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Abstract

Atopic dermatitis is a chronic recurrent skin disorder characterized by severe itching and eczematous skin lesions. Atopic dermatitis is a chronic disease that has various causes and repeats aggravating and improving. It has adverse effects on normal academic, daily life and social relations. In severe cases, many complications occur including mental disorders such as social phobia, and reduced quality of life of other family members. In Korea, atopic dermatitis has been increasing due to rapid changes in living environment due to westernization and industrialization, and it has emerged as a big problem of society. It is a disease that is making a lot of investment in the world and it is pouring new knowledge every year accordingly. Although the individual contents are closely related to each other to make it difficult to distinguish, this article reviews recent findings related to atopic dermatitis by epidemiology, skin barrier, immune deviation, microbiome, psycho-neurology, itch and treatment. I will try to review the development of research in the field of atopic dermatitis in the past year.

Introduction

Atopic dermatitis is a chronic recurrent skin disorder characterized by severe itching and eczematous skin lesions. Atopic dermatitis is a chronic disease that has various causes and repeats aggravating and improving. It has adverse effects on normal academic, daily life and social relations. In severe cases, many complications occur including mental disorders such as social phobia, and reduced quality of life of other family members. In Korea, atopic dermatitis has been increasing due to rapid changes in living environment due to westernization and industrialization, and it has emerged as a big problem of society. It is a disease that is making a lot of investment in the world and it is pouring new knowledge every year accordingly.

Although the individual contents are closely related to each other to make it difficult to distinguish, this article reviews recent findings related to atopic dermatitis by epidemiology, skin barrier, immune deviation, microbiome, psycho-neurology, treatment and itch. I will try to review the development of research in the field of atopic dermatitis in the past year.

1. Epidemiology

There have been many research results on the epidemiology of atopic dermatitis last year.

The relationship between food and atopic dermatitis is an important part of all parents with atopic children. It is well known that the incidence of food allergies is higher in patients with atopic dermatitis, and related studies are continuing. A meta-analysis of papers reported up to 2014 reaffirmed that food allergy is associated with a higher severity of atopic dermatitis[1]. In atopic patients, anaphylaxis due to sensitization through the skin of oatmeal has been reported, which is consistent with the dual-allergen exposure hypothesis that contact through the skin sensitizes the antigen and contact through the diet induces immune tolerance[2]. The aggravation of atopic dermatitis due to food was associated with milk, eggs, peanuts, soybeans, flour, ect. in a retrospective study[3].

The prevalence of atopic dermatitis was higher in children with type 1 diabetes compared to the control group as well as hypertension, hyperlipidemia, depression, and obesity. Itis meaningful because it was the first cohort study to identify the association between type 1 diabetes and atopic dermatitis[4]. In contrast, there is a high risk of rheumatoid arthritis, inflammatory bowel disease, and low risk of type 1 diabetes in patients under 40 years of age with atopic dermatitis[5]. In adults with atopic dermatitis, the risk of autoimmune-related diseases was high such as rheumatoid arthritis, inflammatory growth disease, chronic urticaria, vitiligo and alopecia[6]. In addition, there is a strong interest in the relationship between metabolic disease and systemic inflammatory disease and atopic dermatitis, as there is a report that newborn obesity increases the risk of atopic dermatitis in the cohort study[7].

As a chronic inflammatory skin disease, studies on the similarity and difference between psoriasis and atopic dermatitis have been actively carried out. There is a comparative study in the mouse model. The interesting result has been reported that the 10-year mortality rate of atopic dermatitis is lower than that of psoriasis when comparing in-patients with atopic dermatitis and psoriasis[8,9].

2. Skin barrier

There have been reports that the barrier dysfunction in early childhood may increase the risk of food allergy in the first two years of life in relation to skin barrier function, one of the two factors determining genetic vulnerability of atopic dermatitis[10]. In addition, there has been a report that the acidity of the skin is important in controlling the skin barrier function by Kallikrein 5 in the mouse model. These may be another basis for the use of a weak acid detergent in the management of atopic dermatitis[11].

In one study, it was suggested that acidification of the stratum corneum, obtained by applying acid cream, can prevent the occurrence of asthma due to atopy marching through the mechanism of inhibiting the process of not only the atopic dermatitis itself but also the skin barrier damage leading to the systemic allergic reaction[12].

It is already known that the use of moisturizers from the newborn period has a preventive effect on atopic dermatitis by preventing the deterioration of barrier function and minimizing the effect of exogenous factors of atopic dermatitis. Since ceramide is reduced in the skin of patients with atopic dermatitis, reports that use of physiological lipid-containing moisturizers, such as ceramides, are helpful in improving the skin barrier are still active with the launch of new products. The preventive use of moisturizers is a cost-effective treatment for the management of atopic dermatitis[13-16]. It was reported that petrolatum, a commonly used moisturizing agent, regulates skin barrier function-related gene expression and thereby improves epidermal differentiation.These findings recall the importance of moisturizing agents[17].

3. Immune deviation

Immune dysfunction is an important factor in the pathogenesis of atopic dermatitis as well as skin barrier function abnormality. Among them, the role of T cells in atopic dermatitis is most important, and researches about that are being actively carried out.

The positive correlation between atopic dermatitis and air pollution is well known worldwide.Among the air pollutants, polycyclic aromatic hydrocarbons (PAH) are known to cause inflammation in atopic dermatitis, which is known to activate the transcription factor of AhR (Aryl hydrocarbon receptor). However, it is not known why AhR activity causes Th2 type dermatitis in the skin. In recent study, the expression of arthermin is increased by airborne contaminants, and allergic inflammation reaction occurs through AhR, and there is a positive correlation between AhR activity and ARTN expression in atopic dermatitis[18].

It was found that TSLP (thymic stromal lymphopoietin) in the epidermis of 2 months of age was significant predictor of atopic dermatitis. In addition, intravenous injection of lidocaine, which is commonly used as a local anesthetic, has been reported to be effective in the treatment of atopic dermatitis[19]. Lidocaine intravenous treatment has increased the fraction of FOXP3 mRNA and T reg cells in patients with atopic dermatitis and atopic dermatitis index scores was improved. This is due to the mechanism by which lidocaine stimulates FoxP3 transcription by stimulating TGF-β-induced Smad3 phosphorylation and mitigates the TH1 / TH2 cell and IL-17A / IL-17E cytokine imbalance in patient and mouse models[20].

There was shownthat increased expression of galectin-10 in CD4 + T cells producing IL-22 in patients with atopic dermatitis. Galectin-10 mRNA was previously reported to be elevated in peripheral blood of patients with asthma[21].

There was a report that BOT-4, a benzoxathiol derivative, inhibits STAT protein activation, TCR-mediated Akt gene transfer, and NF-κB signal transduction, thereby demonstrating immunomodulatory activity in

atopic dermatitis and inflammatory skin-like skin similar to psoriasis[22].

In the context of an allergic marathon associated with asthma from atopic dermatitis, studies of Fillagrin depletion, which is often accompanied by a sudden mutation in atopic dermatitis, have been associated with autoimmune dermatitis, irrespective of the adaptive immune system[23]. In addition, there is an effort to search for related genes in patients with atopic dermatitis through genome-wide analysis. Genes related to skin epidermal function and innate / immune function are found[24,25].

The effects of B cell imbalance in atopic dermatitis have not been known yet. Studies on B cell phenotypes in adult atopic dermatitis and psoriasis patients and normal controls have shown that chronic activated CD27 + memory cells and non-switch memory cells are increased[26]. Because early B cell activation may regulate the activity of T cells, further studies in children are needed to clarify the relationship.

4. Microbiome/Environment

Atopic skin is vulnerable to colony formation and infection by Staphylococcus aureus, and about 50% of patients have colonies of Staphylococcus aureus. Staphylococcus aureus can cause severe skin barrier dysfunction, which can promote food allergy in patients with atopic skin through the penetration of the antigen into the skin[27]. In addition, the increase of S. aureus in lesion skin of atopic dermatitis patients was known, but it was also reported to be higher in non-lesional skin than in the control group[28].

In a similar study, 20 strains of bacteria were classified as adult, pediatric, and atopic dermatitis related groups, and only staphylococci were classified as atopic dermatitis-related. Also, the difference in microbiomes between children and adults is analyzed, and it is important to note that the bacterial flour, which is predominantly observed in adult skin, reduces the pH of the skin and increases antibiotic activity, thereby inhibiting the adhesion and growth of the staphylococcus, thereby improving atopic dermatitis or lowering the prevalence of atopic dermatitis[29].

The intestinal flora is itself recognized as an immune system. Song et al. showed that the subtype of Faecalibacterium prausnitzii F06 in the colon of atopic dermatitis patients was increased compared to the normal control group, suggesting a link between the anti-inflammatory butyrate and propionate production[30].

The use of topical antibiotics and systemic antibiotics to reduce colonization of Staphylococcus aureus may reduce the number of bacteria but may not clinically improve symptoms of atopic dermatitis. However, prolonged use may lead to the development of resistant bacteria. In addition, even in the presence of small colonies, it is possible to reproduce, so a novel approach to monoclonal antibodies is expected to be a therapeutic approach against Staphylococcus aureus[31].

5. Psycho-neurology/itch

Itching is a major symptom of atopic dermatitis, and prevention of pathological itching is one of the primary goals of treatment. The itching of atopic dermatitis depends on inflammation and immune response,

so the control of this can be a fundamental therapeutic approach, but there are cases where pathological itching is not controlled by this alone. Because it requires access to the itching pathway, studies are actively carried out on the itch signaling pathway including Tropomyosin receptor kinase A inhibitor (CT327), Janus kinase inhibitor (tofacinib) and κ-Opioid receptor agonist (nalfurafine)[32-35].

In addition, it has been known that epidermal infiltration of peripheral nerve fibers is associated with severe pruritus in atopic dermatitis skin. A three-dimensional analysis of this was made by photon microscopy in 2016. Although the length of the individual nerve fibers in the atopic dermatitis lesion was prolonged compared to the control group, the density and total amount of the nerve fibers were lower than that of the normal control, and the elongated nerve fibers were observed at the disease site but not at the upper part of the epidermis. This suggests that the nerve endings are stimulated by surrounding keratinocytes, but not directly to external environmental stimuli, as a result of some previous studies[36].

6. Treatments

Due to the chronic nature of atopic dermatitis, an annotated letter has been published that reiterates the importance of habit reversal therapy to correct unconscious and habitual scraping behavior in atopic patients[37]. In order to increase the effectiveness of treatment and compliance in clinical practice, appropriate education, psychological and psychological support and treatment should be considered, as well as drugs[38].

Traditionally, topical steroids have been used as a topical treatment for atopic dermatitis, and calcineurin inhibitors have been used as a substitute therapy.

There was an interesting randomized controlled study comparing the effects of topical steroid use on dry skin compared to hydrated skin after bathing. Consequently, no significant difference in efficacy was observed[39]. Since steroid phobia is a global trend, there is a need for a nonsteroidal topical application. So, the results of clinical trials of new drugs have been announced. In 2016, a phase II study of the phosphodiesterase 4 inhibitor, OPA-15406, and a phase III study of two crisaborole, published a paper analyzing the positive results of the efficacy and safety[35,40].

The clinical efficacy of biological agents for the treatment of atopic dermatitis has been reported in the successful treatment of anti IL-31 receptor antibody CIM331 and anti IL-4 receptor antibody Dupiliumab[41-44]. Anti-interleukin-31 receptor A antibody, nemolizumab significantly improved the itching of patients with moderate to severe atopic dermatitis at all monthly doses. This demonstrated the efficacy of the targeted treatment for IL-31 receptor A, but the conclusion of the adverse event is impossible because the size and duration of the trial is limited to 12 weeks[45]. Dupilumab improved the signs and symptoms of atopic dermatitis, including itching, anxiety and depression, and quality of life, compared with placebo in two phase 3 trials of the same protocol for patients with atopic dermatitis[44].

A small cohort survival study of methotrexate (MTX), which has been prescribed off-label for atopic dermatitis, has been published, showing good efficacy and safety in half of the patients, consistent with

previous studies[46].

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References

1. Tsakok T, Marrs T, Mohsin M, Baron S, Du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol 2016;137:1071-1078.
2. Radhakrishna N, Prickett S, Phan T, Rolland JM, Puy R, O'hehir RE. Anaphylaxis to oats after cutaneous sensitization by oatmeal in skin products used for the treatment of atopic dermatitis. J Allergy Clin Immunol Pract 2016;4:152-153.
3. Chang A, Robison R, Cai M, Singh AM. Natural History of Food-Triggered Atopic Dermatitis and Development of Immediate Reactions in Children. J Allergy Clin Immunol Pract 2016;4:229-236.
4. Lin CH, Wei CC, Lin CL, Lin WC, Kao CH. Childhood type 1 diabetes may increase the risk of atopic dermatitis. Br J Dermatol 2016;174:88-94.
5. Schmitt J, Schwarz K, Baurecht H, Hotze M, Folster-Holst R, Rodriguez E, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol 2016;137:130-136.
6. Andersen YM, Egeberg A, Gislason GH, Skov L, Thyssen JP. Autoimmune diseases in adults with atopic dermatitis. J Am Acad Dermatol 2017;76:274-280.
7. O'donovan SM, J OBH, Murray DM, Kenny LC, Khashan AS, Chaoimh CN, et al. Neonatal adiposity increases the risk of atopic dermatitis during the first year of life. J Allergy Clin Immunol 2016;137:108-117.
8. Carretero M, Guerrero-Aspizua S, Illera N, Galvez V, Navarro M, Garcia-Garcia F, et al. Differential Features between Chronic Skin Inflammatory Diseases Revealed in Skin-Humanized Psoriasis and Atopic Dermatitis Mouse Models. J Invest Dermatol 2016;136:136-145.
9. Egeberg A, Skov L, Andersen YM, Mallbris L, Gislason GH, Silverberg JI, et al. Ten-year mortality is increased after hospitalization for atopic dermatitis compared with the general population, but reduced compared with psoriasis. J Am Acad Dermatol 2017;76:98-105.
10. Kelleher MM, Dunn-Galvin A, Gray C, Murray DM, Kiely M, Kenny L, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. J Allergy Clin Immunol 2016;137:1111-1116.
11. Jang H, Matsuda A, Jung K, Karasawa K, Matsuda K, Oida K, et al. Skin pH Is the Master Switch of Kallikrein 5-Mediated Skin Barrier Destruction in a Murine Atopic Dermatitis Model. J Invest Dermatol 2016;136:127-135.
12. Lee HJ, Lee NR, Kim BK, Jung M, Kim DH, Moniaga CS, et al. Acidification of stratum corneum prevents the progression from atopic dermatitis to respiratory allergy. ExpDermatol 2017;26:66-72.
13. Giam YC, Hebert AA, Dizon MV, Van Bever H, Tiongco-Recto M, Kim KH, et al. A review on the role of moisturizers for atopic dermatitis. Asia Pac Allergy 2016;6:120-128.
14. Koppes SA, Charles F, Lammers L, Frings-Dresen M, Kezic S, Rustemeyer T. Efficacy of a Cream Containing Ceramides and Magnesium in the Treatment of Mild to Moderate Atopic Dermatitis: A Randomized,

Double-blind, Emollient- and Hydrocortisone-controlled Trial. Acta Derm Venereol 2016;96:948-953.
15. Norrlid H, Hjalte F, Lundqvist A, Svensson A, Tennvall GR. Cost-effectiveness of Maintenance Treatment with a Barrier-strengthening Moisturizing Cream in Patients with Atopic Dermatitis in Finland, Norway and Sweden. Acta Derm Venereol 2016;96:173-176.
16. Xu S, Immaneni S, Hazen GB, Silverberg JI, Paller AS, Lio PA. Cost-effectiveness of Prophylactic Moisturization for Atopic Dermatitis. JAMA Pediatr 2017;171:e163909.
17. Czarnowicki T, Malajian D, Khattri S, Correa Da Rosa J, Dutt R, Finney R, et al. Petrolatum: Barrier repair and antimicrobial responses underlying this "inert" moisturizer. J Allergy Clin Immunol 2016;137:1091-1102.
18. Hidaka T, Ogawa E, Kobayashi EH, Suzuki T, Funayama R, Nagashima T, et al. The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. Nat Immunol 2017;18:64-73.
19. Kim J, Kim BE, Lee J, Han Y, Jun HY, Kim H, et al. Epidermal thymic stromal lymphopoietin predicts the development of atopic dermatitis during infancy. J Allergy Clin Immunol 2016;137:1282-1285.
20. Li H, Li C, Zhang H, Zhang L, Cheng R, Li M, et al. Effects of lidocaine on regulatory T cells in atopic dermatitis. J Allergy Clin Immunol 2016;137:613-617.
21. Noh S, Jin S, Park CO, Lee YS, Lee N, Lee J, et al. Elevated Galectin-10 Expression of IL-22-Producing T Cells in Patients with Atopic Dermatitis. J Invest Dermatol 2016;136:328-331.
22. Lee HG, Cho NC, Jeong AJ, Li YC, Rhie SJ, Choi JS, et al. Immunomodulatory Activities of the Benzoxathiole Derivative BOT-4-One Ameliorate Pathogenic Skin Inflammation in Mice. J Invest Dermatol 2016;136:107-116.
23. Saunders SP, Moran T, Floudas A, Wurlod F, Kaszlikowska A, Salimi M, et al. Spontaneous atopic dermatitis is mediated by innate immunity, with the secondary lung inflammation of the atopic march requiring adaptive immunity. J Allergy Clin Immunol 2016;137:482-491.
24. Stemmler S, Hoffjan S. Trying to understand the genetics of atopic dermatitis. Mol Cell Probes 2016;30:374-385.
25. Bin L, Leung DY. Genetic and epigenetic studies of atopic dermatitis. Allergy Asthma Clin Immunol 2016;12:52.
26. Czarnowicki T, Gonzalez J, Bonifacio KM, Shemer A, Xiangyu P, Kunjravia N, et al. Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis. J Allergy Clin Immunol 2016;137:118-129.
27. Jones AL, Curran-Everett D, Leung DY. Food allergy is associated with Staphylococcus aureus colonization in children with atopic dermatitis. J Allergy Clin Immunol 2016;137:1247-1248.
28. Tauber M, Balica S, Hsu CY, Jean-Decoster C, Lauze C, Redoules D, et al. Staphylococcus aureus density on lesional and nonlesional skin is strongly associated with disease severity in atopic dermatitis. J Allergy Clin Immunol 2016;137:1272-1274.
29. Shi B, Bangayan NJ, Curd E, Taylor PA, Gallo RL, Leung DY, et al. The skin microbiome is different in pediatric versus adult atopic dermatitis. J Allergy Clin Immunol 2016;138:1233-1236.
30. Song H, Yoo Y, Hwang J, Na YC, Kim HS. Faecalibacterium prausnitzii subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis. J Allergy Clin Immunol 2016;137:852-860.
31. Hepburn L, Hijnen DJ, Sellman BR, Mustelin T, Sleeman MA, May RD, et al. The complex biology and contribution of Staphylococcus aureus in atopic dermatitis, current and future therapies. Br J Dermatol 2016.
32. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol 2016;175:902-911.
33. Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. J Am Acad Dermatol 2015;73:395-399.
34. Elliott G, Vanwersch R, Soeberdt M, Metze D, Lotts T, Stander S, et al. Topical nalfurafine exhibits anti-inflammatory and anti-pruritic effects in a murine model of AD. J Dermatol Sci 2016;84:351-354.

35. Hanifin JM, Ellis CN, Frieden IJ, Folster-Holst R, Stein Gold LF, Secci A, et al. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-controlled study. J Am Acad Dermatol 2016;75:297-305.
36. Tsutsumi M, Kitahata H, Fukuda M, Kumamoto J, Goto M, Denda S, et al. Numerical and comparative three-dimensional structural analysis of peripheral nerve fibres in epidermis of patients with atopic dermatitis. Br J Dermatol 2016;174:191-194.
37. Daunton A, Bridgett C, Goulding JM. Habit reversal for refractory atopic dermatitis: a review. Br J Dermatol 2016;174:657-659.
38. Meadows S, Fending D, Boguniewicz M. Collaboration in best practices for care of patients with atopic dermatitis. J Allergy Clin Immunol Pract 2016;4:347-349.
39. Kohn LL, Kang Y, Antaya RJ. A randomized, controlled trial comparing topical steroid application to wet versus dry skin in children with atopic dermatitis (AD). J Am Acad Dermatol 2016;75:306-311.
40. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol 2016;75:494-503.
41. Nemoto O, Furue M, Nakagawa H, Shiramoto M, Hanada R, Matsuki S, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. Br J Dermatol 2016;174:296-304.
42. Simpson EL, Gadkari A, Worm M, Soong W, Blauvelt A, Eckert L, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). J Am Acad Dermatol 2016;75:506-515.
43. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NM, et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. J Am Acad Dermatol 2016;74:491-498.
44. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of Dupilumab versus placebo in atopic dermatitis. N Eng J Med 2016;375:2335-2348.
45. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, et al. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. N Eng J Med 2017;376:826-835.
46. Politiek K, Van Der Schaft J, Coenraads PJ, De Bruin-Weller MS, Schuttelaar ML. Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis. Br J Dermatol 2016;174:201-203.