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Role of *Staphylococcus aureus* in Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic relapsing, itchy inflammatory condition of the skin usually associated with other allergic diseases such as asthma and hay fever. Following the initial occurrence of AD several factors such as environmental allergens, colonization with Staphylococcus aureus and allergen specific T cell responses are thought to aggravate the disease. The bacteria skin flora of patients with atopic dermatitis is strikingly different from that in healthy people in terms of the presence of Staphylococcus aureus. An altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance and defective cutaneous innate immune response are among various factors contributing to this high bacterial colonization in AD Staphylococcus aureus strains with ability to secrete Staphylococcal enterotoxins A - D and the toxic shock syndrome toxin - 1 have been isolated from the skin of up to 65% of AD patients who are colonized with this microorganism. These toxins aggravate the disease by cellular activation to produce cytokines.

Key words : Atopic dermatitis, *Staphylococcus aureus*, Colonization, Superantigens, T-cells, Cytokines

Introduction

Atopic dermatitis (AD) is a chronic relapsing, itchy inflammatory condition of the skin. It is a common skin disease that is also usually associated with other allergic diseases such as asthma and hay fever. It is thought to affect around 10.7% to 30% of children and 2-3% of adults (Bieber. 2008, Hanifin *et al.* 2007, Sturgill *et al.* 2004). International Study of Asthma and Allergies in Childhood (ISAAC) involving over 196 centres revealed that there has been a dramatic increase of the overall prevalence of AD, asthma and allergic rhinitis (Asher *et al.* 2006). This rise was especially seen with allergic rhinoconjuctivitis (Asher *et al.* 2006). There has also been a 2 to 3 fold rise in AD in industrialized countries where 15 to 30% of children and 2 to 10% of adults are affected (Williams *et al.* 2006).

Although the rise in allergic diseases is higher in developed countries and especially in the temperate climates, a significant increase has also been observed in many countries in Africa (Zar *et al.* 2007). The annual incidence estimates for the 6 to 7 year age group ranged from under 2% in Iran to over 16% in Japan and Sweden (Sugiura *et al.* 1998, Leung *et al.* 1994). Although there is no data on the prevalence of AD in Sri Lanka, the prevalence of all types of dermatitis (which includes AD) was found to be 9.5% in a suburban population in the Colombo district (Perera *et al.* 2000).

AD is associated with disruption of the skin barriers and IgE mediated sensitization to food and environmental allergens (Hanifin *et al.* 2007). The initial mechanisms that induce skin inflammation in patients with AD are not known. However, following the initial occurrence of AD several factors such as environmental allergens, colonization with *Staphylococcus aureus* and allergen specific T cell responses are thought to aggravate the disease (Gong *et al.* 2006, Hanifin *et al.* 2007).

The purpose of this review is to discuss the exacerbation of disease activity by *S. aureus*.

Skin colonization by *S. aureus*

The bacterial skin flora of patients with atopic dermatitis is strikingly different from that in healthy people in terms of the presence of *S. aureus*. The relative rarity (2%-40%) of colonization by *S. aureus* on normal skin sites (Kluytmans *et al.* 1995) is in sharp contrast to the high carriage rate found in patients with AD

ranging from 76% on unaffected areas and up to 100% on acute weeping lesions (Leysen *et al.* 1993). Among various factors contributing to this high colonization of skin by *S. aureus* in AD include an altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance and defective cutaneous innate immune response.

An altered epidermal barrier

The skin of patients with AD tends to be drier due to altered skin lipid content which causes cracking of the skin resulting in transepidermal water loss. The average pH of the skin has shown to be more alkaline, and sphingosine (amino alcohol which forms a primary part of sphingolipids, a class of cell membrane lipids) levels are decreased in both lesional and non lesional stratum corneum, the outermost layer of the skin (Rippke *et al.* 2004, Arikawa et al. 2002). This disruption of the 'normal' skin defenses against bacterial colonization may faciliate colonization with bacteria such as *S. aureus* (Baker. 2006).

Increased bacterial adhesion

Cytokines such as Interleukin-4 (IL-4) produced by Th-2 subtype of T helper cells in the skin of patients with AD, have shown to increase expression of fibronection and fibrinogen, receptors that mediate the adhesion of *Staphylococcus aureus* to stratum corneum (Cho *et al.* 2001). Cytokines are non-antibody proteins secreted by inflammatory leukocytes and some non-leukocytic cells. They trigger inflammation and respond to infections. The cytokines include interleukins, lymphokines and cell signal molecules, such as tumor necrosis factor and interferons.

Defective bacterial clearance

Persistent *S. aureus* colonization is shown to be associated with higher total IgE levels specific to staphylococcal enterotoxin B (SEB) and other enterotoxins (Guzik *et al.* 2005, Breuer *et al.* 2000) because cytokines produced by Th-2 subtype of T helper cells favour development of IgE type antibodies. IgE type antibodies are not good at opsonization and complement activation, which are needed for microbial clearance.

Defective cutaneous innate immune response

The microbe-specific molecules are recognized by Pattern Recognition Receptors (PRRs), proteins expressed by cells of the immune system. Various types of PRRs include the large families of membrane-bound Toll - like

receptors (TLRs) and cytoplasmic NOD - like receptors. The molecules specific for the microbe that are recognized by a given PRR are called Pathogen - Associated Molecular Patterns (PAMPs). PAMPs include bacterial carbohydrates (lipopolysaccharide, mannose), bacterial flagellin, lipoteichoic acid from Gram-positive bacteria, peptidoglycan and nucleic acid variants normally associated with viruses.

Changes in the genes (genetic polymorphisms) that code these PRRs can result in impaired recognition of microbes or an altered or impaired innate immune response. Studies have found genetic polymorphisms in genes that code for TLRs and NOD like receptors in AD (Weidinger *et al.* 2005, Ahmad *et al.* 2004)

Role of *Staphylococcus* superantigens

S. aureus is able to secrete exotoxins with superantigenic properties. Studies have shown that the staphylococcal enterotoxins A-D (SEA-D) and the toxic shock syndrome toxin - 1 (TSST-1) are secreted by *Staphylococcus aureus* strains isolated from the skin of up to 65% of AD patients who are colonized with this microorganism (Llwelyn *et al.* 2002, Bunikowski *et al.* 2000, Bunikowski *et al.* 1999, Nomura *et al.* 1999, Akiyama *et al.* 1996)

Superantigens (SAg) are proteins with powerful immunomodulatory properties. Unlike conventional antigens superantigens do not require processing by antigen-presenting cells to activate T cells. Instead superantigens are presented to T cells by binding to nonpolymorphic regions of class II major histocompatibility complex (MHC) molecules or antigen-presenting cells. Their importance lies in their ability to activate many T cells, resulting in large amount of cytokine production.

Studies show that the amount of serum SAg-specific IgE is correlated with the severity of AD and is strongest when patients produce specific IgE against Staphylococcal enterotoxins originating from *S. aureus* on their skin surface (Bunikowski *et al.* 2000, Strange *et al.* 1996). Staphylococcal Enterotoxins B (SEB), when applied to intact normal skin or the non-lesional skin of patients with AD, can induce erythema and dermatitis and in some AD patients, a flare of the disease in the elbow flexure of the same arm to which the toxin was applied (Michie *et al.* 1996). Development of chronic eczematous dermatitis was seen in patients recovering from toxic shock syndrome caused by TSST-1, but not with patients recovering from Gram-negative sepsis (Michie *et al.* 1996)

In addition to T cells, superatigens can also mediate effects on other cell types such as eosinophils, Langerhans cells, macrophages and keratinocytes (Baker. 2006). During flares of AD, eosinophils are recruited to the skin by chemo attractants where they are activated and the products released by degranulation and cytolytic degeneration promote inflammation and tissue damage (Wedi *et al.* 2002). Superantigens can modulate the effector function of eosinophils by inhibiting eosinophil apoptosis, a programmed sequence of events leading to elimination of cell without releasing harmful substances into the surrounding area (Wedi *et al.* 2002). They also bind to Langerhans cells and macrophages and stimulate them to produce cytokines that up-regulate the expression of adhesion molecules on endothelial cells (Baker. 2006). Further, keratinocytes that have been induced to express MHC Class II molecules by stimulation with Interferon-γ (IFN-γ) can interact with superantigens resulting in the release of pro inflammatory Tumor Necrosis Factor-α (TNF-α) (Ezepchuk *et al.* 1996). Activated keratinocytes enhance antigen presentation to T cells (Nickoloff *et al.* 1993). This has a major impact on AD, due to worsening of T cell mediated immune responses. The capability of superantigens to initiate, exacrbate and maintain inflammation associated with AD can be deduced from these findings.

Clinical implications

Clinical management of AD is aimed at prevention and treatment of flare ups and long term skin care which best suits the individual patient (Bieber. 2008). The cause of recurrent flare ups in AD is not well established. However, in most instances they are usually associated with *S. aureus* infection of the lesions. Therefore, apart from aggressive treatment of these acute episodes with the appropriate topical steroids, emollients, topical calcineurin inhibitors and dressings, treatment of infection with antibiotics which are effective against *S. aureus* is warranted (NICE 2007).

Treatment with a systemic antibiotic such as is usually recommended for a period of 2 weeks with Flucloxacillin or Erythromycin/Clarithromycin of the patient allergic to Flucloxacillin or the organism is resistant to it. Topical antibiotics may be used if the infection is localized. However, topiacl antibiotics should not be for more than 2 weeks because of the development of antibiotic resistance (NICE 2007). Currently, the long term use of antibiotics is not recommended as the benefit of such treatment has not been established.

Conclusion

Atopic dermatitis (AD) is a chronic relapsing, itchy inflammatory condition of the skin usually associated with other allergic diseases such as asthma and hay fever. It is commoner among children than among adults. The bacterial skin flora of patients with atopic dermatitis is strikingly different from that in healthy people in terms of the presence of *S. aureus*. An altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance, and defective cutaneous inate immune response are among various factors contributing to this high colonization of skin by *S. aureus* strains with ability to secrete toxins, aggravates the disease by cellular activation to produce cytokines.

Reference

Ahmad-Nejad, P. Mrabet-Dahbi. S Breuer K. (2004). "The Toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. "J-Allergy-Clin-Immunol 113(3): 565-7.

Akiyama, H. Toi, Y. Kanzaki, H. (1996) "Prevalence of producers of enterotoxins and the toxic shock syndrome toxin-1 among *Staphylococcus aureus* strains isolated from atopic dermatitis lesions." Arch Dermatol-Res 288(7): 418-20.

Arikawa, J. Ishibashi, M. Kawashima, M. Takagi, Y. Ichikawa, Y. Imokawa, G. (2002). "Decreased levels of sphingosine, a natural antimicrobial agent, may be associated with vulnerability of the stratum corneum from patients with atopic dermatitis to colonization by *Staphylococcus aureus*." J-Invest-Dermatol 119(2): 433-9.

Asher, M.I. Montefort, S. Bjorksten, B. Lai, C.K. Strachan, D.P. Weiland, S.K. (2006). "Worldwide time terends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys." Lancet 368(9537): 733-43.

Baker, B.S. (2006). "The role of microorganisms in atopic dermatitis." Clin-Exp-Immunol 144 (1): 1-9.

Bieber, T. (2008). "Atopic dermatitis." N. Engl-J-Med 358(14): 1483-94.

Breure, K. Wittmann, M. Bosche, B. Kapp, A. Werfel, T. (2000) "Severe atopic dermatits is associated with sensitization to Staphylococcal enterotoxin B (SEB)". Allergy 55(6): 551-555.

Bunikowski, R. Mielke, M. Skarabis, H. (2000) "Evidence for a disease promoting effect of *Staphylococcus aureus* - derived exotoxins in atopic dermatitis" J -Allergy-Clin-Immunol 105(4): 814-19.

Bunikowski, R. Mielke, M. Skarabic, H. (1999). "Prevalence and role of serum IgE antibodies to *S. aureus*-derived superantigens SEA and SEB in children with atopic dermatitis." J-Allergy-Clin-Immunol 103(1): 119-24.

Cho, S.H. Strickland, I. Tomkinson, A. Fehringer, A.P. Gelfand, E.W. Leung, D.Y. (2001). "Preferential binding of *Staphylococcus aureus* to skin sites of Th-2 mediated inflammation in a murine model." J-Invest - Dermatol 116(5): 658-63.

Ezepchuk, Y.V. Leung, D.Y. Middleton, M.H. Bina, P. Rieser, R. Norris, D.A. (1996). "Staphylococcal toxins and protein A induce cytotxicity and release of tumor necrosis factor from human keratinocytes." J-Invest-Dermatol 107(4): 603-9.

Gong, J.Q. Lin, L. Lin, T. Hao, F Zeng, F.Q. Bi, Z.G. (2006). "Skin colonization by *Staphylococcus aureus* in patients with cezema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial." Br-J-Dermatol 155(4): 680-7.

Guzik, T.J. Bzowska, M. Kasprowicz, A Czerniawska-Mysik, G. Wojcik, K. Szmyd, D. Adamek-Guzik, T. Pryjma, J. (2005). "Persistent skin colonization with *Staphylococcus aureus* in atopic dermatitis: relationship to clinical and immunological parameters." Clin-Exp-Allergy 35(4): 448-55.

Hanifin. J.M. Reed, M.L. (2007). "A population-based survey of eczema prevalence in the United States." Dermatitis 18(2): 82-91.

Kluytmans, J.A. Mouton, J.W. Ijzerman, E.P. (1995) "Nasalcarriage of *Staphylococcus aureus* as a major risk factor for wound infections after cardiac surgery." J-Infect-Dis 171(1): 216-219.

Leung, R. Ho, P. (1994). "Asthma, Allergy and atopy in three south-east Asian populations." Thorax 49(12): 1205-1210.

Llwelyn, M.C. Cohen, J. (2002). "Superantigens: microbial agents that corrupt immunity. Lancet-Infect-Dis 2: 156-162.

Lyden, j.L. Marples. R. Kligman, A.M. (1993). "*Staphylococcus aureus* in the lesions of atopic dermatitis." Br-J-Dermatol 90(5): 525-530.

Michie, C.A. Davie, T. (1996). "Atopic dermatitis and Staphylococcal superantigens." Lancet 3: 347-324.

NICE (2007) "Atopic eczema in childern - Management of atopic eczema in childern from birth upto the age of 12 years. "National Institute for Health and Clinical Excellence: NICE clinical guideline 57.

Nickoloff, B.J. Mitra, R.S. Green, J. Shimizu, Y. Thompson, C. Turka, L.A. (1993). "Activated keratinocytes present bacterial-derived superantigens to T. Lymphocytes:

relevance to psoriasis." J-Dermatol-Sci 6(2): 127-33.

Nickoloff, B.J. Mitra, RS. Green, J. Zheng, X.G.. Shimizu, Y. Thompson, C. Turka, L.A. (1993). "Accessory cell function of kerationocytes for superantigens. Dependence on lymphocyte function-associated antigen-1/intercelluar adhesion molecule-1 interaction." J-Immunol 150: 2148-2159.

Nomura, I. Tanaka, K. Tomita, H. (1999). "Evaluation of the *Staphylococcus* exotoxins and their specific IgE in childhood atopic dermatitis" J-Allergy-Clin-Immunol 104: 441-6.

Perera, A. Atukorale, D.N. Sivayogan, S. Anyaratne, V.S. Karunaratne, L de A. (2000) "Prevalence of skin diseases of Sri Lanka." Ceylon Medical Journal 45: 123-8.

Rippke, F. Schreiner, V. Doering, T. Maibach, H.I. (2004). "Stratum corneum pH in atopic dermatitis: impact on skin barrier function and colonization with *Staphylococcus aureus*." Am-J-Clin-Dermatol 5: 217-23.

Starange, P. Skove, L. Lisby, S. Nielsen, P.L. Baadsgaard, O. (1996). "Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. Arch-Dermatol 132: 27-33.

Sturgill, S. Bernard, L.A. (2004). "Atopic dermatitis update. Curr-Opin-Pediatr 16(4): 396-401.

Sugiura, H. Umemoto, N. Deguchi, H. Murata, Y. Tanaka, K, Sawai, T. Omoto, M. Uchiyama, M. Kiriyama, T. Uehara, M. (1998). "Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: comparison with the disease frequency examined 20 years ago." Acta-Derm-Venereol 78: 293-294.

Wedi, B. Wieczorek, D. Stunkel, T. Breuer, K. Kapp, A. (2002). "Staphylococcal exotoxins exert proinflammatory sffects through inhibition of eosinophil apoptosis, increased surface antigen expression (CD11, CD45, CD54 and CD69), and enhanced cytokine-activated oxidative burst, thereby triggering allergic inflammatory reactions." J-Allergy-Clin-Immunol 109: 477-84.

Weidinger, S. Klopp, N. Rummler, L. (2006). "Association of NOD1 polymorphisms with atopic eczema and related phenotypes." J-Allergy-Clin-Immunol 116: 177-84.

Williams, H. Flohr, C. (2006). "How epidemiology has challenged 3 prevailing concepts about atopic dermatitis." J-Allergy-Clin-Immunol 118: 209-13.

Zar, H.J. Ehrlich, R.I. Workman, L. Weinberg, E.G. (2007). " The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002." Pediatr-Allergy-Immunol 18(7): 560-5.