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아토피성 질환관리의 최신 동향

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= Abstract =

Recent Progress in the Care of Atopic Disease in Children

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Background: Atopic dermatitis starts as an early childhood type1 hypersensitivity to environmental allergens and is often the first step in the atopic march to develop into asthma and allergic rhinitis. Despite progress that has been achieved in management, this health problem remains poorly controlled and cause great pain and suffering for many children and their parents. **Purpose:** To introduce nurses to recent progress in pathophysiology, management and preventive measure of atopic disease. **Search method:** Systemic search was done using the PubMed and CINAHL from 1980 to 2005. In addition, historical references were taken from standard medical textbook. **Results:** In total, 30 relevant publications were located including primary research and review articles that cover the pathophysiology, management, and preventive measure of atopy. The evidence emerging from literature indicate that non-medical approaches such as breastfeeding and probiotics would improve management outcomes. **Conclusion:** The review suggests that breastfeeding and probiotic approaches would be the most effective preventive measures for children with atopic diseases.

Key words : Atopic, Hypersensitivity, Immunoglobulin E, Probiotics

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Introduction

Allergy is one the most common disorder we see or hear daily at home or at clinic nowadays. The term 'allergy' was coined for the first time by von Pirquet describing hypersensitivity reaction(as cited in Roitt, Brostoff, & Male, 1996). Hypersensitivity is an immune response, occurring in an exaggerated, inappropriate and unusual form. The first historical experimentation of allergy took place in 1921 in which Prausnitz took serum from Küstner, who was allergic to fish and injected into own skin. When fish extract was subsequently inoculated to the same "serum-inoculated" site, there was an immediate wheal and flare reaction. Prausnitz postulated from this experiment the existence of an "reagin" in Küstners' serum. This "reagin" is nowadays the very IgE antibody. In 1923, Coca and Cook(as cited in Roitt et al., 1996) used the term "atopy" for the first time describing the clinical profile of allergy. Atopy is used as the umbrella term covering eczema, asthma, hay fever, urticaria and food allergy, and allergy, atopy and type 1 hypersensitivity have been interchangeably used.

Atopic dermatitis starts out during early infancy(within 2 month after birth) as an eczema around face and head, and subside within short period, however it can persist into or start in adolescence or early adulthood. The lifetime prevalence of atopic dermatitis is 10-20% in children and 1-3% in adults (Novak, Bieber, & Leung, 2003).

Its prevalence has been increased two to three folds during last three decades in industrialized countries(Spergel & Paller, 2003). At the same time, mechanisms underlying pathogenesis of atopy have been elucidated. We begin gradually to understand complex interactions of susceptibility genes and inflammation eliciting cytokine genes and allergy eliciting antibody gene(IgE), as well as interactions among susceptibility genes and the host's environment(Leung, Boguniewicz, Howell, Nomura & Hamid, 2004). On the other hand, clinical and epidemiological studies revealed to us numerous allergens as well as adjuvant factors, such as tobacco smoke, air pollution and infections(Sengler, Lau, Whau, & Nickel, 2002).

The aim of the review was to introduce the pathophysiology, current management and preventive measures of atopic disease to nurses. The author conducted a systemic search method using the PubMed and CINAHL from 1980 to 2005 as well as a classical pediatric textbook. Used search terms were, atopic disease, atopic dermatitis, hypersensitivity, IgE and probiotics.

The result of review was organized into four sections: section I, atopy as IgE mediated typel hypersensitivity, deals various faces of allergic reactions; section II, described new anti-allergic drugs; section III, summarized genes associated with atopy and section IV, discussed prevention of atopic disease in childhood including nursing implication in which author tried to present potential roles of nurses in the prophylactic intervention.

Methods

The databases, PubMed and CINAHL, were searched using key words that included atopic disease, atopic dermatitis, hypersensitivity, IgE, probiotics, and nursing. The searches were restricted to human studies and written in English for the period of 1980- 2005. In addition, a standard immunology textbook was consulted. The search included primary research as well as review articles. The author located a total of 62 articles. However, many of these were too medically oriented or treatment oriented and so were excluded. Thirty publications met the inclusion criteria: Nineteen were primary researches and the remaining eleven were review papers or textbook.

Results

Atopy as an IgE mediated type I hypersensitivity

- Atopy as a type I hypersensitivity

According to a standard textbook of immunology(cited in Roitt et al., 1996), originally IgE antibodies are produced against parasitic infections. This antibody had been beneficial and protective to human ancestors who had been constantly beseized by the parasites. However, to contemporary human living in relatively parasite-free environment, IgE antibodies produced against nonparasitic agents are unnecessary and nuisance to the host. A certain types of antigens are called allergen, because they induce IgE antibodies. Those IgE antibodies bind to the IgE receptors on the surfaces of mast cells as well as basophilic leukocytes. Both mast cells and basophils store a large number of vesicles filled with vasoactive molecules. When an atopic child is exposed to the same allergen later, these allergen molecules bind now the

IgE-coated mast cells and basophils and trigger the release of vasoactive mediator molecules which cause in minutes vasodilation and smooth muscle contraction. The outcome may be local or systemic, depending on the extent of mediator release. Clinically, consequences of type I hypersensitivity can range from life-threatening anaphylaxis such as penicillin allergy and asthma to intolerably annoying conditions such as eczema, urticaria and hay fever.

● Atopy as a systemic anaphylaxis

Systemic anaphylaxis is a fatal shock-like condition which occurs within minutes. This life threatening phenomenon was first observed by Portier and Richet in dogs after injection of antigens(as cited in Roitt et al., 1996). A wide range of antigens are known to induce systemic anaphylaxis in susceptible human, including the venom from bee, wasps, hornet, and ant stings; certain drugs such as penicillin, insulin, and antitoxins; and seafood and nuts. The drug of choice for these situations is epinephrine which counteracts the effects of vasoactive mediators such as histamine and the leuckotrienes, a mediator of inflammation. Epinephrine acts by relaxing the smooth muscles, reducing the vascular permeability as well as improving cardiac output. This systemic anaphylaxis, a horrifying accident, occurs in a few minutes and causes death of the allergic patients. It could be preventable by simple inquiry on past exposure and readily available epinephrine(as cited in Roitt et al., 1996).

● Atopy as localized anaphylaxis

Atopy is manifested as a localized anaphylactic reaction. The reaction is limited to a specific target tissue or organ, often involving epithelial surfaces at the site of allergen entry. They are atopic dermatitis(eczema), food allergy, allergic rhinitis, asthma and others.

Manifestations of allergic reactions are related to the biological effects of the mediators during the degranulation of primary effectors such as mast cell or basophil. These mediators act on local tissue as well as on secondary effector cells such as eosinophils, neutrophils, T lymphocytes, monocytes, and platelets. Therefore clinical picture can vary depending on the extent and location of the immune responses.

Systemic or localized hypersensitivity reactions are due to the mediators contained in the granules of mast cell or basophils including histamine, serotonine, chemotactic factors and proteases(protein degrading enzymes). However, even far more potent mediators, the leukotriens and prostaglandins are generated from the enzymatic breakdown of phospholipids in the plasma membrane of those effector cells. The leukotrienes mediate bronchial constriction at nanomolar concentration. For example, in case of penicillin allergy in human, bronchial and tracheal smooth muscle contraction appears at first to be mediated by histamine, but, within 30-60 seconds, further contraction is induced by the leukotrienes and prostaglandins, and that induce the prolonged bronchospasm. The type 1 hypersensitivity reactions become even more complex by the variety of cytokines released from mast cells and eosinophils. Human mast cells secrete IL-4, IL-5, IL-6, and TNF-α Particularly, IL-4 is required for the IgE production(as cited in Roitt et al., 1996).

As for the pathophysiology of atopic dermatitis, it is characterized by dryness and increased transepidermal water loss. The major water-retaining component in the extracellular space of epidermis is a matrix of structural proteins linked to ceramides(lipid like molecule). Reduction of ceramide content of atopic skin has been reported(Sator, Schmidt, & Honigsmann, 2003). This impairment of barrier function leads to increased susceptibility to irritants as well as increased absorption of allergens. At least two types of atopic dermatitis are recognized: An "extrinsic" form associated with IgE-mediated sensitization accounting for 70-80% of the atopic patients, and an "intrinsic" form without IgE-mediated sensitization involving 20-30% of the atopic patients (Novak et al., 2003). Both forms of atopic dermatitis showed infiltration of eosinophils. Extrinsic form of atopy, is characterized by marked infiltration of type 2 helper T cell within skin.

● Atopic march

Among the infants suffering from atopic dermatitis, some with allergic genetic background progress into a systemic disease such as allergic rhinitis or asthma, and persist in childhood and young adulthood. Such progression is called "atopic march or allergic march." If the early intervention fails to identify the allergen or mismanage the disease, allergy march is unavoidable. Atopic skin as compared to non-atopic skin, contains an increased number of IgE-binding Langerhans dendritic cells(antigen presenting cell) which migrate to the lymph node to stimulate naïve T cells(antigen unexposed cell) to expand into helper T cells(antigen exposed cell). Original

IgE mediated atopic dermatitis thus develops into a complex T cell disease which signals the first step in atopic march(Novak et al., 2003).

New anti-allergic drugs

The obvious first step of the management of atopic dermatitis is to identify the allergen and to avoid contact to it. Skin hydration and use of emollient to repair skin barrier function is a key part of management. For stubborn atopic dermatitis, repeated injections of increasing doses of allergen(so-called hyposensitization therapy) has been used. However, knowledge of the mechanism of mast cell degranulation and the mediators involved in this disease opened the way to drug therapy. Anti-histamine has been the most frequently used drug for urticaria and epinephrine is a life-saving medication for the systemic anaphylaxis. Corticosteroids offer by far the most effective treatment available for the control of allergic disease. Corticosteroids mediate their anti-inflammatory effects through binding of glucocorticoid receptor(GCR) in target cells. Corticosteroid bound GCR interact to inhibit various transcription factors which will transcribe numerous proinflammatory cytokine and chemokine genes that amplify and perpetuate allergic inflammation. However, due to the concerns about potential side effects associated with chronic use, topical corticosteroids have not been used for maintenance therapy, especially non-lesional skin, in atopic dermatitis.

Several new generations of anti-allergic drugs have been introduced(Table 1). A humanized monoclonal antibody to IgE, which reduces profoundly circulating IgE concentrations, has been found to provide surprising benefit in patients with severe steroid-dependent asthma. Tacrolimus and pimecrolimus are calcineurin inhibitor and block T cell signaling and have been used as the immunosupressant in the transplantation surgery. Topical use of Tacrolimus and pimecrolimus demonstrated sustained efficacy without any noticeable side effects, therefore, they are safely used for facial and eyelid eczema(Boguniewicz, Eichenfield & Hultsch, 2003). Alternatively, UV-light therapy has been useful for chronic stubborn atopic dermatitis. Targets of the UV-therapy are inhibition of cytokine secretion by Langerhans cells and keratinocytes.

Genes associated with atopy

Major achievement in atopy research during last two decades has been the identification of chromosomal regions and polymorphisms of atopy related genes. Twin studies have shown concordance rates of 0.72-0.86 in mozygotic, 0.21-0.23 in dizygotic, twin pairs, demonstrating a genetic basis for atopy-related trait(Cookson & Moffatt, 2002). However, atopy-associated phenotypes are complex traits probably caused by an interaction of multiple disease susceptibility genes and environmental factors. It may take another decade of research to elucidate the mechanisms of these gene-gene interaction or susceptibility factor-environmental factor interactions and racial differences in the prevalence of atopy.

Management of atopic disease in childhood: Nursing implication

A large number of twin studies and family analyses strongly suggested a genetic basis for atopy-related traits(e.g., Cookson, 2004). It became also evident during the course of genetic studies that a significant part of the genetic determination of allergic disease, particularly asthma depends on the environmental factor that trigger the disease(Patino & Martinez, 2001). The documented increase in prevalence of allergic

<Table 1> New generation of anti-allergic drugs

Category/drug	Therapeutic targets
Anti- Allergy approaches	
Anti-IgE antibodies	Blocking of IgE
Allergen-selective immunotherapy	Allergen avoidance
Anti-T cell approaches	Desensitization
Alefacept	Blocking of T cell activation
Efalizumab	Blocking of T cell-APC interaction
Anti-Inflammatory Agents	
Oral pimecrolimus	Inhibition of TH2 cytokine secretion
TNF inhibitors	Inhibition of inflammatory TNF signaling
Chemokine antagonists	Blocking of recruitment of inflammatory cell by chemokines

disease over the last 25 years in the industrialized countries is likely due to changes in lifestyle and environment rather than change in atopy related genes, because it would take generations for genetic interbreeding to explain such magnitude of increase in prevalence(Spergel & Paller, 2003). The prevention of atopy may be possible through the change of lifestyle and preventive intervention can be initiated as early as fetal or newborn stage. Mothers can avoid potential allergens through careful diet, breastfeeding for their infants, and even to try out probiotic approaches.

● Breastfeeding

Recent research showed a protective effect of exclusive breastfeeding over 4 months against childhood eczema, atopy, and bronchial asthma(Dell & To, 2001; Kull et al, 2005; Oddy et al., 1999). Breast milk is rich in long-chain polyunsaturated fatty acids which includes γ-linolenic acid(GLA), arachidonic acid(AA), eicosapentaenoic acid(EPA), and docosahexaenoic acid(DHA)(Das, 2002). Those long-chain polyunsaturated fatty acids have variable actions on immune response and in the secretion of proinflammatory cytokines. Human breast milk not only supports the somatic growth and development but also helps the development of immune system. Both EPA and DHA are known to affect the expression of gene families governing the cytokines, receptors, signal transduction pathways, transcription factors, cell cycle, repairs, apoptosis, DNA synthesis, cell adhesion, cytoskeleton, and hormone receptors as assessed by microarray technique (Verlengia et al, 2004). The two factors, long-chain polyunsaturated fatty acid content of breast milk and duration of breast-feeding account for differences in the incidence of atopy (Das, 2002). Nurse as a lactation specialist can contribute to the prevention of allergic disease in this area.

● Windows of allergen exposure

• In utero

As mentioned in the section of 'atopy as a systemic disease,' 70-80% of atopic dermatitis appears to be triggered by the environmental allergens. The uterus is the first environment in which life form undergo developmental pathways. Accordingly, in utero exposures to certain chemicals may have the potential to produce long-lasting effects. Maternal smoking during pregnancy is a major in utero exposure that is associated with poor fetal and infant outcomes and increased wheezing and asthma in children. This finding was confirmed in a Finnish birth cohort study that included almost 60,000 children(Jaakkola & Gissler, 2004). There are several other factors to be considered when assessing the effects of in utero exposures on the risk of developing allergy and asthma, however certain factors were confirmed by the replicated researches whereas certain other factors are not verified yet. For example, cord blood IgE levels are inversely correlated with birth order and highest in first-born neonates(Ball et al., 2000). Pregnancy, delivery by cesarean section and infections in early infancy are risk factors for childhood allergy and asthma, whereas maternal diet supplementation with high level antioxidants and maternal allergen exposure during pregnancy and their in utero effects to childhood allergy and asthma are still equivocal(Katz, Pocock., & Strachan, 2003; Oddy et al., 1999)

• Childhood

Atopy is one of the most common chronic childhood diseases and the mean duration of the symptoms is 2 years (Dell & To, 2001). Atopic dermatitis is often the initial step in the so-called "atopic march," which leads to asthma, food allergy and allergic rhinitis. There are several predictive factors of "march of atopy." Some of them are genetic traits and physiological background, others are environmental factors(Table 2). Parental allergy history is an index of genetic susceptibility to atopy and asthma(Sibbald, Horn, Brain, & Gregg, 1980). Eighty percent of children with two asthmatic parents develop the disease whereas 10% of children with no asthmatic parent develop the asthma. Male children showed 2 to 4 times higher frequencies of asthma(Yunginger et al., 1992). Numerous cross-sectional epidemiological studies indicated an increased prevalence of asthma in the overweight children and adolescents in the United States. A large epidemiological survey(Thomson, Clark, & Camargo, 2003) indicated that over 75% of asthmatic patients visiting emergency department were obese or overweight. The mechanistic relationship between obesity and asthma or atopy has been studied using mouse model of the disease and relying on some human epidemiologic studies. Increases in serum leptin(leptin is the product of obesity gene, and secreted by adipose tissue) observed in obese subjects may contribute to the increased incidence of asthma because leptin belongs to IL-6 family of cytokines and has proinflammatory effects, thereby exacerbate asthma in the obese.

Due to the global economic development of the past 50 years, home environment has changed enormously with the high-rising apartment living, central heating and soft furnishings. Indoor ventilation has decreased with considerable increase both in humidity and in concentrations of indoor pollutants and allergens. Make the situations worse, most people spend more than 99% of their lives indoors, therefore indoor air is the major source of allergens. Accordingly, allergen avoidance becomes the primary prevention of atopic diseases.

In the late 1980s, as the results of the literature survey of air pollution and respiratory infections, a strong inverse relationship between household size and hay fever was discovered in a cohort in the United Kingdom(Strachan, 1989). Contrary to the prevailing viewpoint that respiratory infection induces asthma, Strachan postulated that, children raised among large family build up immunity against various minor infections and this immunity must have protective effect against development of allergic disease. This theory was colloquially called the "hygiene hypothesis." In support of "hygiene hypothesis," several epidemiological studies showed a reduced prevalence of hay fever, asthma, and atopy in rural dwelling children from farming families in comparison with non-farming rural families(Braunfahrlander et al. 2002). The challenge for the future research will be to find out the balance of type 1 helper T cell and type 2 helper T cell immunity in childhood through epidemiological studies and to be able to modify the environment to reduce the prevalence of atopic disease through the environmental engineering without causing harm to susceptible individuals. Perhaps, probiotic approach might serve as the environmental engineering in an immunological sense.

● Probiotics

In 2001, The Food and Agriculture Organization(FAO) and World Health Organization(WHO) have made statement that there is adequate scientific evidence to indicate that there is potential for probiotic foods to provide health benefits and that specific strains are safe for human use(FAO/WHO, 2001). An expert panel commissioned by FAO and WHO defined probiotics as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host.' Prototype of probiotic food has been the 'Yogurt,' the milk product fermented by lactobacillus. Even today, lactobacillus is the most popular and trusted probiotic microorganism in use. Various strains of lactobacillus have been investigated for the industrial application and used mostly as the probiotics for infantile diarrhea of newborns and children, and for vaginitis or for gastroenteritis caused by Helicobacter pylori of adults (Reid, Jass, Sebulsky, & McCormick, 2003). The application of probiotics for the prevention of atopic disease has been ongoing for last several years in Canada, Denmark, Finland and Australia. All of the investigators employing lactobacillus strains gave daily orally as a capsule for 4 weeks to 18

<Table 2> Risk factors associated with atopy in the childhood.

Parental Factor (Sibbald et al.,1980)
80% of children with two asthmatic parents will develop asthma
40% of children with one asthmatic parents will develop asthma
10% of children with no asthmatic parents will develop asthma

Gender Factor (Yunginger et al., 1992)
Male develops asthma 2 to 4 times more frequently than female in the first 3 years of life

Endocrine Factor (Thomson, Clark, & Camargo, 2003)
Obesity is associated with increased prevalence of atopy or asthma

Environmental Factor
Maternal smoking during pregnancy, odd ratios 1.25-1.35
(Jaakkola & Gissler, 2004)
Indoor-allergens (Woodcock & Custovic, 1998)
Environmental allergens (Strachan, 1989)
Occupational allergens among 10-25% of adults (Arif, Delclos, Whitehead, Tortolero, & Lee, 2003)

Psychological Factor
Psychological stress (Nield & Cameron, 1985)

months to the atopic children, and evaluated the clinical improvement using the scoring atopic dermatitis score. All reported that probiotics was effective in the management of atopic dermatitis(Kalliomaki, Salminen, Poussa, Arvilommi, & Isolauri, 2003). The probiotic organisms seem to reverse increased intestinal permeability, enhance IgA responses, promote gut barrier function through restoration of normal flora. However, further mechanistic and epidemiological researches are required to draw definite conclusion. Lastly, we may even be able to rely on alternative medical approach to control stubborn atopic dermatitis(e.g., Kobayashi, Takahashi, Mizuno, Kutsuna, & Ishil, 2004).

Conclusion

Last two decades of research on atopy has elucidated various aspects of the pathophysiological mechanisms, discovered gene-environmental interactions, and introduced new anti-allergic drugs. Epidemiological research has revealed various risk factors for allergy and showed useful preventive interventional strategies. In spite of these achievements, atopic disease remains as one of the most annoying disorders, particularly for children. Preventive measures such as change of lifestyle or elimination of environmental factors or development of probiotic approaches might be the next best choice for these children. Nurses are the frontline manpower in the healthcare system not only for management but also for the prevention. Nurses can promote self-care, treatment adherence, and can help children with atopic disease to cope more effectively with their illness.

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