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Review Article

Allergic asthma in children: Inherited, transmitted or both?

(The transmission of periodontopathic bacteria concept)

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ABSTRACT

 Background: *In theory, allergic diseases including asthma, was the result of exposure to a transmissible agent and do not depend on early infection which is said to make children more allergy-resistant. This seems, to be a direct contradiction to the hygiene hypothesis, since epidemiologic evidence can be cited in this theory's support. The fact that nearly all children with asthma are allergic, but only a small proportion of allergic children have asthma, at least raises the possibility that some additional factor is involved. That this additional factor might be a transmissible agent is also suggested by the similarity between the gross epidemiologic patterns of children with paralytic poliomyelitis in the 1950s and children with asthma currently.* **Purpose:** *The purpose of this study was to reveal the possible relationship between the transmissions of allergic asthma and periodontopathic bacteria.* **Reviews:** *Recent researches showed that periodontopathic bacteria are transmissible from mother and caregivers to infants. In addition, a collaborated research that was conducted by dental practitioners and pediatricians revealed that Gram-negative bacteria were significantly predominant (p = 0.001) in uncontrolled allergic asthmatic children compared to well-controlled ones. Nevertheless, how does these two phenomenon related was still uncertain. Literatures showed that periodontopathic bacteria modulates host immune response and sometimes caused disadvantageous effect to allergic asthma.* **Conclusion:** *According to the ability of periodontopathic bacteria and its components to stimulate immunocompetent cells, it is possible that they are able to modify host-immune response which tends to increase allergic asthma symptoms.*

Key words: *transmission, allergic asthma, periodontopathic bacteria, children*

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INTRODUCTION

The "hygiene hypothesis" proposes that the increase in allergic diseases in developing countries reflects a decrease in infections during childhood. Cohort studies suggest, however, that the risks of asthma are increased in children who suffer severe illness from a viral respiratory infection in infancy. This apparent inconsistency can be reconciled through consideration of epidemiologic, clinical, and animal studies. The elements of this line of reasoning are that viral infections can predispose to organ-specific expression of allergic sensitization, and that the severity of illness is shaped by the maturity of immune function, which in turn is influenced by previous contact with bacteria and viruses, whether pathogenic or not.[1]

Clinical studies of children and interventional studies of animals indeed suggest that the exposure to microbes through the gastrointestinal tract powerfully shaped immune function.[1,2] In addition, the initial microbial exposure for children born by Caesarean section is delayed compared with those born by vaginal delivery; epidemiological studies revealed that Caesarian section[3,4] and preterm[5,6] infants have more asthma risk.

Coincidentally, the periodontopathic bacteria in dental plaque are also transmissible. Some studies showed that if a child harbored a periodontal pathogen, then at least one of the parents will exhibit the same genotype of bacteria.[7] Tanner *et al.*[8] found that various anaerobic species colonize the edentulous mouths of infants, and that maternal or caregivers saliva may act as a source of some

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Gram-negative anaerobes.[7] Regarding to allergic diseases which has T-helper2 (Th2), or Type 2 immune response, not as other pathogens, Gram-negative periodontopathic bacteria, especially their lipopolysaccharides (LPS) have a unique characteristics; in some instance enhance the Type 1 immune response [i.e. LPS from *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* (high dose)]; nevertheless, low dose of *P. gingivalis* LPS enhance the Type 2 immune response.[9–12]

A study by Wiyarni *et al.*[13] revealed that dental plaque control therapy improves respiratory quality and that the asymptomatic asthmatic children had significant lower Gram-negative positive culture than uncontrolled asthma (wheezing and coughing) in one week study. Evaluation of randomly selected subjects after two months revealed that their asthmatic symptoms and food allergy also diminished.[14] Therefore, there is a possibility that asthma is not merely inherited, but also transmissible, whether by transmission of virus, periodontopathic bacteria or both.

The purpose of this review was to sketch the rationale for a new theory of asthma's pathogenesis. The proposed theory is that asthma is caused, at least in part, by infection, especially in infancy, by a respiratory virus, most likely a human rhinovirus (HRV) only or concomitantly with periodontopathic bacteria such as *P. gingivalis* The understanding of this review may help dental practitioners, especially pediatric dentist to answer questions conducted by medical practitioners, especially pediatric allergy specialist regarding the possible connection between oral hygiene and allergic asthma.

Atopic and non-atopic asthma

Atopy is a personal and/or familial tendency to, usually in childhood or adolescence, become sensitized and produce immunoglobulin E (IgE) antibodies in response to ordinary exposure to low doses of allergens, usually proteins.[15] Atopy can be detected by specific serum IgE or skin-test reactivity to environmental allergens, is often associated with asthma. The prevalence of atopy has increased over time in some populations, whereas in others there has been a decrease or a plateau in prevalence since 1990. Asthma and atopy can occur either independently or jointly in patients, in populations, and over time. In the United Kingdom and Australia, the prevalence of both asthma and skin-test reactivity has increased, whereas in Hong Kong, Germany, and Italy, the prevalence of atopy but not of asthma has increased.[15] In some populations, the prevalence of asthma associated with allergies has increased more than that of non-atopic asthma, whereas in others the prevalence of the two types of asthma has increased to a similar degree. Until today it is still not known what factors cause asthma in a person with atopy or what factors cause atopy in a person with asthma.[1,15,16] Several "new" factors also increase asthma risk, that are Caesarian section[3,4] and pre term birth.[5,6]

The "hygiene hypothesis" for the increase in prevalence of allergic disease

The proportion of people affected by allergic diseases, including allergic rhinitis eczema, and asthma, has increased dramatically over the past 50 years. The increase has been most marked in children, and was first noted in developed, "Westernized" countries. These diseases remain relatively uncommon in poor rural populations, but have increased sharply in such populations on migrating to urban areas or to regions of high prevalence. Multiple different theories have been proposed to account for this phenomenon, with many focusing on differences in diet or in childhood exposure to allergens, like house dust mite, cockroach, and molds trapped in indoor air by Western patterns of housing. The theory that has held up best so far, the "hygiene hypothesis," was first put forward by Strachan when he noted an inverse association between family size and the rate of allergic disease, with the greatest protection being associated with the number of older siblings.[1,17]

Asthma as a transmissible disease

A theory, seemingly in direct contradiction to the hygiene hypothesis, is that allergic diseases, including asthma, are the result of exposure to a transmissible agent, either virus (HRV) or microbes. As for the hygiene hypothesis, epidemiologic evidence can be cited in this theory's support. On the simplest level, the fact that nearly all children with asthma are allergic, but only a small proportion of allergic children have asthma, at least raises the possibility that some additional factor is involved. That this additional factor might be a transmissible agent is also suggested by the similarity between the gross epidemiologic patterns of children with paralytic poliomyelitis in the 1950s and children with asthma currently. Both are more common among children of small, well-off families and among children migrating to urban areas from rural ones.[1]

On a smaller scale, the pattern of asthma's penetration into native populations also seems consistent with exposure to a transmissible agent. Among the Fore people of New Guinea, asthma appeared first in adults returning to villages after working in a European influenced city. Only thereafter did it appear in children; and another has found the rates of asthma to be nearly as high in adopted children of mothers with asthma as in natural children.[1]

Microbial colonization and risk of atopy

There are a number of unique features of immune responses during this early period. Pregnancy is associated with complex interactions at the materno-fetal interface, which reduce cell-mediated tissue rejection and Type 1 (IFN-γ) immune responses. An increase in type 2 immune activity is among a number of mechanisms evolved to protect the fetus in this context. At birth, the cellular responses of the fetus continue to reflect this 'type 2' skewed pattern. Whether due to immaturity or active type 1 regulation (or both), the neonatal capacity for IFN-γ responses is significantly impaired compared with those of

adults, resulting in an increased vulnerability to infection during his period. In this context it is clear that intrauterine infection is associated with increased capacity for neonatal type 1 responses, confirming that antenatal exposures have the potential to influence maturation of type 1 function, which tends to be non-allergic. Thus, it is possible that 'cleaner environments' could be having an effect even before birth.[9,17]

The effect of clean environment before birth had been studied by Roduit et al.[3] and Thavagnanam et al.[4] who reported that Caesarean section may have contributed to the rise in asthma. The mode of delivery has been reported to influence the development of allergic diseases in childhood. The prevalence of allergies and asthma in childhood has increased dramatically over the past few decades, mostly in industrialized countries. In parallel, rates of Caesarean delivery have risen in most of the developed countries, from about 5% in the 1970s to over 30% in 2000 in some regions of the world. The initial microbial exposure for children born by Caesarean section is delayed compared to those born by vaginal delivery; thus the maturation of the immune systems might be different and delayed.

Especially their is a finding that the risk of asthma and allergy is lower in adults with serologic evidence of infection with microbes transmitted by the "orofecal" route. Taken together, these observations suggest a protective effect not of viral infection, but of microbial exposure in a broader sense, including nonpathogenic microbes. This idea, that exposure to nonpathogenic microbes might play a role in preventing the development of asthma and other allergic diseases, was greatly advanced by studies of stool flora in infants from populations with different rates of allergic disease.[1]

Role of bacteria in asthma

Toews[18] review revealed that *Mycoplasma pneumoniae* and *Chlamydophila. pneumoniae* may be associated with asthma chronicity. The role of *M. pneumoniae* and *C. pneumoniae* infections with chronic asthma has been evaluated using PCR, culture and serology to detect *M. pneumoniae*, *C. pneumoniae* and viruses. Altogether, 56% of asthmatic patients had a positive PCR for *M. pneumoniae* or *C. pneumoniae*. Positive results for PCR were found in broncholaveolar lavage (BAL) fluid or biopsy samples. Cultures for these organisms were negative in all patients. Asthma risk showed by significantly greater number of tissue mast cells were noted in the group of patients who were PCR positive.

Effect of dental plaque control therapy on respiratory quality

Wiyarni et al.[13] study in 30 children (7-11 years old) with mild persistent asthma revealed significant predominance of Gram-negative bacteria cultures in uncontrolled asthmatic children (i.e. wheezing, coughing at night) compared to controlled asthma (asymptomatic), and significant increase of respiratory quality based on forced expiratory volume in one second (FEV1) (p = 0,001; CI 95%) in asthmatic

children with dental plaque control therapy compared to without dental plaque control therapy after one week study. Furthermore, randomly selected subjects did not manifest asthmatic symptoms after two months evaluation.[14]

Transmission of periodontopathic bacteria

Despite the abundance of commensal bacteria present in the birth canal, none of these are able to successfully colonize the mouth of the infant suggesting that they do not have tropism for the oropharyngeal mucosa. It has been proposed that bacteria are transferred from the primary caregiver, external environment, and from other areas of the respiratory tract. Successful colonization depends on the ability of the bacteria to circumvent host innate and acquired immunity in order that they can adhere to oral surfaces and avoid removal via the flushing action of saliva and mastication. Neonatal saliva has been shown to contain secretory immunoglobulin A (SIgA) antibodies that react with these bacteria, but these antibodies appear insufficient to completely block adherence and subsequent colonization.[19]

It was unclear whether the initial colonization by periodontal pathogens occured in the oral cavity. McClellan et al.[20] reported the association between specific age groups and the time when the initial colonization by periodontal pathogens occurs in the oral cavity in such groups. According to this study and a study by Tanner et al.[8], *P. gingivalis* was detected in all age groups, even among children less than 1 year of age. The youngest child whom *P. gingivalis* was identified was 20 days old, and three of the six predentate infants in the sample population were positive for *P. gingivalis*. These data suggest that *P. gingivalis* was acquired rapidly upon exposure, even in the first days of life, and before what has been assumed to be its primary ecological niche, the gingival sulcus, has developed.[8,20]

The role of parents and caregivers in bacteria transmission

Studies showed that if a child harbored a periodontal pathogen, then at least one of the parents will exhibit the same genotype of bacteria found that various anaerobic species colonize the edentulous mouths of infants, and that maternal saliva may act as a source of some Gram-negative anaerobes. A simple but reliable test is needed in routine clinical examinations to identify the presence of bacteria associated with periodontal diseases.[7,21]

BANA test

The BANA (N-benzoyl-DL-arginine-2-naphthylamide) test detects a trypsin-like enzyme that is present in *P. gingivalis*, *Treponema denticola*, and *Tannerella forsythensis*. The BANA test had 92% sensitivity and 70% specificity when compared with DNA probes and polyclonal immunological reagents and children whose parents were colonized by BANA-positive bacteria were 9.8 times more likely to be colonized by BANA-positive species than were children whose parents were BANA-test-

negative. Children whose parents had clinical evidence of periodontitis were 12 times more likely to be colonized by BANA-positive species. These data are compatible with the hypothesis that children may acquire the BANA positive species from their parents, especially if the parent has periodontitis.[7]

A study revealed that 70 of the 140 caregivers tested BANA-positive and/or weakly positive in one or more of the quadrants. Eighty-four percent of children whose caregivers were BANA-positive were also BANA-positive, whereas only 7% of children whose caregivers were BANA-negative were BANA-positive. Sixty-three percent of the children aged 3–5 yrs and 92% of the children aged 6–10 yrs, whose caregivers were BANA-positive, were also BANA-positive. If caregivers or family members had a history of periodontal disease, the children were significantly more likely to be BANA-positive. Forty-seven children (62%) whose caregivers were > 35 years old had BANA-positive scores, while only 26% of children who had younger caregivers had BANA-positive scores.[7,21]

BANA test was done by taking plaque samples with toothpick then wiped onto the lower strip of the BANA card. A separate toothpick was used for each plaque sample. After all tooth sites had been sampled, the upper strip was lightly moistened with distilled water by means of a cotton swab. The BANA card was folded at the perforation mark, so that the lower and upper strips met and placed in an incubator at 55° C for 5 min. The BANA card was removed, and the lower portion was discarded in a manner appropriate for contaminated material. The color on the upper strip was recorded by consensus of two different examiners, as 'no blue' (negative), a 'faint blue' (weakly positive), or a 'distinct blue' (positive). For statistical analysis, weakly positive and positive results were recorded as positive.[7]

The role of antimicrobial therapy in asthma

Infection has been thought to be responsible to asthma exacerbations, therefore there has been much progress in understanding the mechanisms of microbe-induced asthma exacerbations, and the development of new therapeutic agents as well as preventive strategies is needed. Both antimicrobial and immune modulators could have therapeutic benefits in this respect. Several different antibacterial agents, namely tetracyclines, macrolides, quinolones, azalides and the ketolide telithromycin have in vitro and in vivo activity against the common atypical bacteria *C. pneumoniae* and *M. pneumoniae*. They have shown some clinical benefit in patients with chronic stable asthma or acute exacerbations.[22]

DISCUSSION

Schroder and Arditi[23] reported that infectious diseases have a major impact on both the development and the severity of asthma. The rise of asthma in industrialized countries over the last decades has been attributed to increased hygiene standards as well as the concomitant use of antibiotics, which together lower the incidence of infection. Although this point of view is supported by both clinical studies and experimental approaches in mice, an increasing body of evidence suggests that certain infectious diseases may predispose for the development of asthma, thus challenging the `hygiene hypothesis'.

The effects of bacteria on immune development are likely to be the greatest in the postnatal period when the infant has more direct contact with environment. The first years of life through the gradual maturation of type 1 responses, although this appears not to consolidate until after 18 months of age so that responses during this early period are relatively skewed towards the type 2 which normally characterized allergic disease. However, despite this, the majority of infants do not go on to develop atopy. Although it has not been confirmed, there has been longstanding speculation that an important contributing factor in the development of type 2 immune disease is delayed development of type 1 function by bacterial exposure in infancy. A reduction in the level and variety of early microbial burden is an obvious candidate in the search for culprits in the spiralling levels of allergic disease.[1,18] This concept was supported by Roduit et al.[3] and Thavagnanam et al.[4] study that Caesarean section may have contributed to the rise in asthma.

It is well-known that the etiopathogenesis of allergy is multifactorial i.e. genetics, environmental and allergens factors.[1] However, it is still unclear why oral focal infection may involve in allergic development and symptoms. It is interesting that preterm birth also increases asthma risk,[5,6] and coincidentally, even still inconsistent, previous epidemiological studies revealed that periodontal disease increases preterm birth risk. Nevertheless, a study by Katz et al.[24] in 2009 by using immunocytochemistry, identified the presence of *P. gingivalis* antigens in placental tissues. The antigens were detected in the placental syncytiotrophoblasts, chorionic trophoblasts, decidual cells, and amniotic epithelial cells, as well as the vascular cells. These results suggest that *P. gingivalis* may commonly colonize placental tissue, and that the presence of the organism may contribute to preterm delivery. Thus periodontopathic bacteria may indirectly cause allergy, by inducing preterm birth.

The role of infection in asthma etiopathogenesis is in accordance with Pejcic et al., and Paju et al.[25] and Scannapieco et al.[26] who showed that oral focal infection can play a part in the creation of respiratory infections that manifest as sinusitis, tonsillitis, pneumonias, bronchial asthma. These diseases can be caused by microorganisms from the oral cavity, following a direct inhalation from saliva and dental plaque, or by blood dissemination.[25] There have also been numerous other descriptions of the mechanism where oral bacteria have been included in the pathogenesis of respiratory infections, i.e. *P. gingivalis* and *A. actinomycetemcomitans* which can aspire into the lungs and cause infection (droplets infection); then the host`s and bacterial enzymes from the saliva can dissolve saliva pelicula on pathogens and allow them to adhere to the surface of mucous membrane; and also cytokines derived from the

periodontal tissue can damage the respiratory epithelium by causing an infection via respiratory pathogens. Damage of respiratory epithelium may lead to increased sensitivity to respiratory allergens or stimulation.[25,26]

Even though respiratory infection is proposed as one of the pathways that periodontopathic bacteria may involved in asthma transmission etiologies; nevertheless, the exact mechanism is still uncertain. It is logical that transmission of periodontopathic bacteria to infants may result from maternal or caregiver's saliva, thus increases respiratory infection risk (via droplet infection) by touching with dirty hands, kissing, or via using the same spoon, glass or plate that are not sterilized.[7,21,27] However it is interesting that according to Guilbert et al.[28] study on breast feeding by asthmatics may increase the risk of asthma in babies born to mothers with the respiratory disease; and Leme et al.[29] stated that mice pups born to normal mothers and breastfed by asthmatic foster mothers develop airway hyperresponsiveness and eosinophilic airway inflammation. In addition, Perez et al.[30] study revealed that breast milk is not always free of bacteria.

It is also supported by the predominance of Gram-negative bacteria in dental plaque of uncontrolled asthmatic children that had been verified in Wiyarni et al.[13] study. However, in Toews'[18] review, periodontopathic bacteria were not included in asthma pathogenesis; it was not surprising because according to Yilmaz,[31] these bacteria are able to internalized gingival epithelial cells, thus could not be detected easily. Nevertheless, recently, not only the whole periodontopathic bacteria had to be confirmed for their presence, their enzymes could also detected with the BANA test.[21] Therefore, the verification of the the hypothesis that periodontopathic bacteria may involved in asthma etiopathogenesis and exacerbation is possible. Moreover, improving personal hygiene and treatment of periodontal diseases of mothers and caregivers is mandatory. Several precautions were thorough cleaning or aseptic of breast area before breastfeeding; and sterilizing bottle or feeding set. Thus also the bad habits of blowing for cooling of hot foods for the infants and children.

For the concluding remarks, periodontopathic bacteria may involve in asthma transmission via several ways: direct transmission from parents and caregivers via inducing respiratory infection and Type 2 immune response; indirectly via placenta and inducing preterm birth. Additionally, for research needs, BANA test for parents and caregivers is a beneficial diagnostic test for the possibility of periodontopathic bacteria transmission in asthmatic children with unknown etiology. However, further collaborated research of allergy specialists and dental researchers are mandatory to verify this concept.

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