Symposium 1: What do we learn from birth cohort study?

Psychologic stress and allergic disease: Brain-gut-microbiome axis

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Allergic diseases such as asthma, atopic dermatitis, food allergy, and allergic rhinitis are some of the most common chronic diseases in the world. In the past few decades, the global prevalence of these diseases is continuing to rise particularly in Asia including Korea.

During the same period, Korea has experienced rapid economic growth marked by industrialization, modernization, urbanization, technological achievement, high education levels, and greatly improved living standards. These changes have resulted in rapid changes in the life styles such as residential environment and the population's culture, dietary habits and hygiene.

In human development, prenatal period is the most critical period in terms of function and structure. The developmental origins of health and disease (DOHaD) hypothesis postulates that all organ systems undergo developmental programming *in utero* that shapes the physiology and metabolism of the adult. Indeed, there are multiple lines of evidence which suggests that exposure to various environmental variables *in utero* and during early childhood may play a major role in susceptibility to allergic diseases.

The COhort for Childhood Origin of Asthma and allergic diseases (COCOA) birth-cohort study is currently underway. It is designed to investigate the causal contribution of the following five environmental factors to the development and natural course of allergic diseases: (1) perinatal exposure to indoor factors (namely, house-dust mites, bacterial endotoxins, tobacco smoking, and particulate matter 2.5 and 10), (2) perinatal exposure to outdoor pollutants, (3) perinatal maternal psychosocial stress, (4) perinatal nutrition, and (5) the perinatal microbiome. Thus, the COCOA study will help to delineate how these environmental factors interact with each other and the genetic background of the child during this critical time point in the child's life.

There is little evidence to support an association between symptoms of pediatric allergic disorders and psychosocial factors in the general population, particularly in Asian countries. We conducted a Child

Behaviour Checklist on elementary school children with ages ranging from 7 to 11 and found that externalizing problems were significantly larger in children with asthmatic symptoms, while internalizing problems were significantly larger in children with symptoms of both asthma and allergic rhinitis. Social adaptations were significantly lower in children with symptoms of allergic rhinitis and atopic dermatitis. While school children with allergic symptoms have been reported to have more difficulties with psychosocial adaptation, the patterns of psychosocial problems varied somewhat according to the types of atopic disorder, such as higher internalizing problems in children with asthma and AR.

We also investigated the relationship between three major allergic diseases, asthma, allergic rhinitis (AR), and atopic dermatitis (AD), and psychological and behavioral problems in 780 preschoolers based on a community survey. Scores for internalizing and sleep problems were significantly higher in those diagnosed with AR. Preschoolers who had been treated for AD in the past 12 months had higher attention problem and attention-deficit/ hyperactivity disorder scores. Sleep problems were more severe in moderate to severe AD compared to control and mild AD groups, categorized according to SCORing index of AD. These findings suggest that psychological and behavioral problems differed among the three major allergic diseases, weaker association for asthma and stronger association for AR and AD. The results of this study may lead to the identification of potential underlying shared mechanisms common to allergic diseases and psychological and behavioral problems.

Recent evidence suggests that prenatal maternal distress increases the risk of allergic diseases in offspring. However, the effect of prenatal maternal depression and anxiety on AD risk remains poorly understood. We investigated whether prenatal maternal distress is associated with AD risk in offspring, and whether the mechanism is mediated by reactive oxygen species (ROS). We found that prenatal maternal distress increased the risk of AD in offspring (hazard ratio for depression, 1.31 [95% CI, 1.02-1.69]; anxiety, 1.41 [1.06-1.89]). Prenatal maternal depression and anxiety scores were positively related to the predicted probability of AD. Prenatal distress decreased placental GSH/GSSG ratios, and especially in those who later developed AD, decreased placental 11β-HSD2 levels and increased IgE levels at 1-year-old. These findings suggest that prenatal maternal depression and anxiety promote the risk of AD in offspring. The mechanism may involve chronic stress, abnormal steroid levels, and ROS.

Furthermore, environmental stressors such as negative life events (NLEs): separation or divorce, death of a close relative or friend, financial problems, marital problems, experience of involuntary job loss or partner's job loss, and problems with the children during pregnancy significantly increased offspring's AD symptoms during the last 12 months (aOR, 1.61; 95% CI 1.12-2.31) and AD treatment during last 12 months (aOR, 1.57; 95% CI 1.05-2.34).

Environmental causes including maternal factors before or during pregnancy such as infection, diet, medication, delivery mode, and stress and those after delivery such as feeding, use of antibiotics, and infection, may affect the development of microbiota and immune response of offsprings. However, the exact

mechanism underlying the association between prenatal maternal stress and AD is poorly understood. Recent data indicate that changes in the composition of the gut microbiota influence the development of AD. The prevailing view is that the gut and brain are connected via the microbiota and that the composition of the gut microbiota in patients with major depressive disorders is different to that in healthy controls. We investigated possible mechanisms through which prenatal stress causes development of AD in offspring via the gut microbiota. We found that prenatal maternal depression or anxiety was associated with AD and the proportion of *Enterococcus* was the highest in infants with AD whose mother had high STAI (State-Trait Anxiety Inventory) score. These results provide clear clues about a connection between maternal stress and AD in infants.

Tremendous progress has been made in characterizing the bidirectional interactions between the central nervous system, the enteric nervous system, and the gastrointestinal tract. A series of provocative preclinical studies have suggested that the gut microbiota appears to influence the development of emotional behavior, stress- and pain-modulation systems, and brain neurotransmitter systems. Additionally, microbiota perturbations by probiotics and antibiotics exert modulatory effects on some of these measures in adult animals. Current evidence suggests that multiple mechanisms, including endocrine and neurocrine pathways, may be involved in gut microbiota-to-brain signaling and that the brain can in turn alter microbial composition and behavior via the autonomic nervous system. Limited information is available on how these findings may translate to healthy humans or to disease states involving the brain or the gut/brain axis. Future research needs to focus on confirming that findings from animal studies are translatable to human physiology and to diseases such as irritable bowel syndrome, autism, anxiety, depression, Parkinson's disease, allergic diseases.

In summary, prenatal maternal stressful conditions regardless of severity of impact affect the development of allergic diseases. Our understanding of the possible mechanisms explaining maternal stress response in the fetus still lacks causality, and further investigation is needed. Environmental factors affecting early life microbiota including prenatal maternal stress in critical period are important to develop allergic diseases and shape immune development, which provides new individualized approaches to the prevention of allergic diseases. In future, the mechanism of gut-brain axis should be investigated.

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