Abstract. – The prevalence of asthma and allergic diseases in childhood has increased in several industrialized countries since the second half of the twentieth century. In some countries, the prevalence is still rising, although in others it seems to have plateaued or even decreased. It has been suggested that environmental factors operating prenatally and in early life affect the development of asthma and allergic diseases. Particularly changes in microbial exposure are proposed to play an important role in the development and maturation of the immune system. Thus, the factors that affect microbial exposure, such as mode of delivery and the use of antibiotics, may influence the development of asthma and allergic diseases. Several studies have explored the associations between perinatal factors and children’s use of antibiotics and the risk of asthma, with inconsistent findings.

The present review article will be focused on the important findings related with factors responsible for above allergic reactions along with asthma in young infants. Also, the influence of cow milk intake will also be taken thin account to cover the aspect of cow milk induced allergies and asthma in infants.

Key Words: Allergy, Infants, Asthma, Genetics, Cow milk allergy (CMA).

Introduction

The food allergy and asthma are the most common chronic conditions in childhood. The prevalence of asthma and allergic diseases like allergic rhinitis in childhood has shown an increasing trend in several industrialized countries since the second half of the twentieth century1. In some countries, the prevalence is still rising, although in other countries the prevalence seems to have declined2. The development of asthma and allergic diseases has a strong genetic background. The rise in the prevalence of these diseases indicates that environmental factors also play an important role as well3.

The gut microbiota plays an important role in the maturation and development of the immune system. The popular “microflora hypothesis” suggested that perturbations in the gastrointestinal microbiota as a result of reduced microbial exposure result in immature microbiota, which might delay proper maturation of the immune system, and the resulted delay usually led to an increase in asthma and allergic diseases4. The factors that have been suggested to be related to the development of asthma included infections, non-pathogenic microbes, dietary factors, exposure to tobacco smoke, air pollutants and allergens5. Also a report in recent past6 suggested that various factors related to pregnancy, delivery and fetal growth also contributed significantly to the above pathological state. Despite active research, evidence on early life factors and the development of asthma is not consistent. Further, evidence on the role of environmental factors in the development of CMA or any food allergy is limited. Identification of risk and protective factors for CMA, asthma and other allergic diseases is important for prevention strategies. Although not all early life factors are easily modifiable, identification of such factors may help focus preventive strategies on children at high risk. So, the present review article is the first of its kind to review maternal background factors, perinatal factors, and the maternal use of antibiotics factor associated with the development of cow’s milk allergy and asthma in childhood. The article shall help medical researchers, physicians working in area to get an overall concise updated overview of the present condition and shall help in better planning of future research for the efficient management of these pediatric pathological states.

Cow Milk allergy (CMA) – an Overview

The allergy is defined as a hypersensitivity reaction initiated by specific immunologic mechanisms7. Cow’s milk allergy (CMA) is defined...
as an adverse clinical reaction to ingested cow’s milk proteins based on an immunologically mediated adverse reaction to the provoking proteins at doses which are tolerated by healthy persons. Exposure to cow’s milk proteins provokes an immune response in all infants, although in healthy infants the response is suppressed and oral tolerance is developed. On the other hand, if oral tolerance is not achieved, inflammatory mediators will be activated and released in several organs. Mechanisms of CMA are best understood and described in antibody-mediated, (immunoglobulin E [IgE]-mediated) CMA, while the precise immunologic mechanisms of cell-mediated (non-IgE mediated) CMA remains less clear. In IgE-mediated CMA typical symptoms, which usually develop rapidly within minutes or an hour after ingestion of cow’s milk protein, included skin like urticaria and angioedema respiratory symptoms like wheeze, and anaphylaxis. In non-IgE-mediated CMA, symptoms tend to have later onset, from few hours to days after ingestion of cow’s milk protein. The most commonly affected area in this case is the gastrointestinal tract. There is a consensus that the diagnosis of food allergy has to be based on oral food challenge procedures that establish a causal relation between the ingestion of a particular food and a subsequent clinical reaction. Of the different challenge procedures, double-blind placebo-controlled food challenge is considered the “golden standard” of diagnosing food allergies. However, only a minority of studies related to CMA has used this procedure and, in epidemiological research, CMA is often defined as either parentally reported or oral food challenge confirmed CMA.

**Asthma**

Asthma is defined as a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyper-responsiveness. A key component in the pathology is chronic inflammation and various factors such as viruses, allergens and exercise. These factors also responsible for hyper responsiveness, inflammation together with hyper-reactivity associated with airway obstruction. Asthma can present with symptoms such as recurrent episodes of wheezing, coughing, shortness of breath, and chest tightness. In epidemiological research, according to Spycher et al., most frequently used asthma or wheeze phenotypes are based on 1) triggers/short-term temporal pattern (including exclusive viral wheeze and multiple-trigger wheeze), 2) long-term temporal pattern (including early transient wheeze, persistent wheeze and late-onset wheeze), 3) presence of allergic sensitization (atopic asthma and non-atopic asthma) or 4) severity (including wheeze and asthma). In children, the occurrence of recurrent wheezing episodes is a universally accepted starting point of asthma diagnosis. In addition to medical history, methods to establish asthma diagnosis include physical examination, evaluation of lung function, atopy, airway inflammation, bronchial hyper-responsiveness and exclusion of alternative diagnosis. In young children, the asthma diagnosis is particularly challenging due to difficulties in applying objective lung function measurements. Thus, in infants and preschool-aged children, the diagnosis is often based on medical history and symptoms.

**The Role of gut Microbiota in the Development of Asthma and Allergic Diseases**

The gut microbiota is a major source of microbial exposure, containing an assortment of micro-organisms inhabiting the entire gastrointestinal tract. Colonization of the human gut microbiota begins immediately at birth, as upon passage through the birth canal infants are exposed to a complex microbial population. After the initial establishment of the gut microbiota during the first year of life, the composition of gut microbiota is host-specific, evolving throughout an individual’s lifetime, and is susceptible to both exogenous and endogenous modifications. Stimuli derived from normal gut microbiota have been demonstrated in experimental studies to be important in facilitating the development of oral tolerance to food allergens and tolerance to inhaled aeroallergens. The idea of the potential role of gut microbiota in the development of allergic diseases has encouraged several observational studies to assess the association between the gut microbiota composition and allergic diseases. Although an association between the gut microbiota composition and various allergic conditions or symptoms has been reported, no specific harmful or protective microbes have been identified yet. Further, there has been a substantial effort to assess the effects of probiotics, living micro-organisms that exert health benefits, on the prevention and or treatment of allergic diseases in clinical trials. Moreover, there is a theoretical basis for probiotics to have a positive beneficial effect in allergy prevention or treatment evidenced in some studies but not all studies have reached the same conclusions.
Cow Milk Associated Genetic Factors linked with Allergy and Asthma

Despite active research, the causes of asthma and allergic diseases are only partially understood. Heredity is a generally accepted important risk factor, but the rise and international variation in prevalence rates are likely attributable to environmental aspects and gene-environment interactions. Whether food allergies and asthma share same genetic and environmental factors or whether there are some unique factors to each disease is still unclear. Family history and twin studies have indicated that genetics plays an important role in the development of asthma and food allergies. Nearly 100 genes have been found to be associated with asthma or asthma-related phenotypes, although not all of these associations could have been replicated in further studies. Unlike asthma, only a limited number of genetic studies – namely candidate gene association studies – of food allergies have been reported. Polymorphisms in nine genes have been associated with food allergy or food allergy severity in at least one study, but most of these associations have not been replicated. Some of the genes associated with food allergy are also associated with asthma, although the relevance of these genes to both food allergy and asthma together remains to unexplored.

Environmental Factors and the Allergies

The priming of the immune system occurs in early childhood or even before birth has prompted the idea of a “critical time-window” for environmental factors to come into play and impact the development of asthma and allergic diseases. Knowledge of the role of different environmental factors in the development of CMA or any food allergy remains limited, but more extensive research has been conducted on the associations between different environmental factors and the development of asthma in childhood. The factors that have been suggested to be associated with the development of asthma included microbial infections, dietary factors, and exposure to tobacco smoke, air pollutants and allergens. As the mother is an exclusive environment for the child for the first nine months and after birth continues as the closest caregiver, she can be considered as a major environmental factor operating for the child’s development. Thus, various factors related to prenatal period, i.e. pregnancies as well as deliveries have received growing attention.

Infections and non-Pathogenic Microbes Associated with Allergies

Infections in early childhood have been implicated in the development of asthma, although their role is complex. For example, severe lower respiratory tract infections have been associated with an increased risk of asthma, while repeated viral infections have been reported to be associated with a decreased risk. Further, indirect measures of infections like the care of a child in a daycare centre and high number of older siblings have been shown to be associated with both a decreased and an increased risk of asthma. Despite the fact that severe lower respiratory tract infections have been linked to later development of asthma, it is still unclear whether these lower respiratory tract infections caused subsequent development of asthma or whether these infections merely mark individuals that have a genetic propensity for developing asthma. Further, it has been suggested that qualitative aspects of infections such as timing, type and intensity may be crucial in the development of asthma. There is currently no evidence that infections would play a major role in the development of cow’s milk allergy or any food allergy in early childhood. Furthermore, not only pathogenic microbes causing symptomatic infection, but also non-pathogenic microbes have been suggested as playing a role in the development of asthma and allergic diseases. Several studies have shown that exposure to environmental microbes is inversely associated with the risk of asthma and allergic diseases; for example, a lower prevalence of asthma and atopy has been observed in a population with higher number of bacterial exposures compared to a population with lower exposure despite these two populations living in geographically adjacent areas. Further, a lower prevalence of asthma and allergic diseases among children living on a farm has been found repeatedly, and the largest reduction in risk has been demonstrated for those exposed to a farming environment both prenatally and post-natally until adulthood. In addition, an observation that microbial diversity of house dust was inversely related to the prevalence of childhood asthma independently of farming status and that a lower environmental biodiversity in the surroundings of study subjects’ homes was more common in atopic than in nonatopic adolescents. This emphasizes the role of overall microbial exposure and environmental biodiversity in the development of asthma and allergic diseases.
Diet Factors in Allergies/Asthma

Breast milk, one of the most important early nutritional sources in the postnatal period, contains compounds with immune modulatory properties, and has been hypothesized to be protective for the children against asthma and allergic diseases. Several studies support this idea of protective role of exclusive breastfeeding until at least four months of age, but the discussion on the preventive effects of breastfeeding continues, mainly due to methodological issues. The role of complementary feeding in the development of allergic diseases has been revised in recent years. Delaying exposure to solid foods or avoidance of allergenic foods in infancy is no longer recommended for prevention of allergic diseases. In fact, evidence that early introduction of certain foods is beneficial in decreasing the risk of asthma and allergic diseases is emerging. On a nutrient level, it has been hypothesized that changes in antioxidant intake, the ratio of dietary n-6:n-3 polyunsaturated fatty acids, and vitamin D might play a role in the development of asthma and allergic diseases. Observational studies have reported inverse associations between asthma and n-3 polyunsaturated fatty acids and dietary antioxidants in the postnatal diet, although supplementation of infants’ diet with fish oil or vitamin D have so far failed to show any major benefit. A maternal intake of antioxidant rich foods, fish oil and vitamin D during pregnancy has been reported to be inversely associated with wheezing, asthma and other allergic diseases in the offspring. In addition, limited intervention data suggested that some benefits of fish oil supplementation during pregnancy in reducing the risk of allergic disease in offspring.

Maternal Factors for Cow’s Milk Allergy and Asthma

Maternal age at delivery has been observed to be inversely associated with the risk of asthma in two studies, directly associated in one study (Juhan et al 2005), and not associated in two studies. Studies by McKeever et al and Bråbäck et al found age-dependent associations; the inverse association was stronger or present in children diagnosed with asthma at early ages, whereas the association was weaker or not present in children diagnosed at older ages.

Evidence on the role of exposure to smoking on the development of various food allergies is limited. A birth cohort study explored infant feeding patterns as well as subsequent immunological patterns of CMA proving no association between maternal smoking during pregnancy and CMA in the infant. On the contrary, maternal smoking during pregnancy is a generally accepted risk factor for respiratory symptoms, reduced lung function, and a 20%-68% increased risk of asthma. In a study in the recent past, an increased risk of asthma was observed in children diagnosed with asthma at early ages, whereas no association was observed in children diagnosed at older ages.

Perinatal Factors

In perinatal factors the mode of delivery matters to some extent. Two meta-analyses have recently summarized the association between delivery by caesarean section and the risk of asthma. Both meta-analyses concluded that delivery by caesarean section was associated with a roughly 20% increase in the subsequent development of asthma compared with vaginal delivery. In addition, some studies have reported a higher risk of asthma in children born by assisted vaginal delivery compared with children born by normal spontaneous vaginal delivery, whereas also null association with assisted vaginal delivery has been reported.

Evidence on fetal growth and the risk of CMA and other food allergies is limited. Low birth weight has been associated with a decreased risk of food allergy, but also no association between low birth weight and/or gestational age has been reported. Liem et al assessed the role of high birth weight on food allergy, but they failed to find an association. On the contrary, several studies have explored associations between gestational age and birth weight and the risk of asthma, with inconsistent findings.

Effects of Antibiotics Usage

Antibiotics are natural or synthetic drugs which inhibit microbial growth or kill microbes such as bacteria. An increased risk of asthma or wheeze in the offspring who were exposed to antibiotics prenatally was observed in earlier studies. A largest cohort study reported a 10% increased risk of asthma in children whose mothers were non-asthmatic and had used antibiotics during pregnancy. In a study, by Stensballe et al the strongest association was observed for macrolides. Also, Stensballe et al observed that maternal antibiotics for both non-respiratory infections and other indications were associated with an increased risk of asthma.

Children’s use of antibiotics and the subsequent development of asthma or wheeze have been explored more extensively. The major outcome of...
these studies\textsuperscript{49,50} was that exposure to antibiotics during the first year of life was related with an increased risk of asthma in childhood, but the association was significantly stronger in retrospective studies than in prospective studies. Recently, two systematic reviews\textsuperscript{48,51} concluded that exposure to antibiotics was associated with a weak increase in risk of asthma or wheeze. The largest studies assessing the dose-response effect of antibiotics\textsuperscript{48,51,52} reported a 30\% to 99\% increased risk of asthma in children exposed to antibiotics five, six or more times during early childhood. Age-dependent associations have been observed in some studies: the association between exposure to antibiotics and the risk of asthma was found to be stronger in children diagnosed at early ages, but not in children diagnosed at older ages\textsuperscript{51}.

Conclusions
So, this can be concluded from the review that external feeding including Cow’s milk is one of the prominent cause of paediatric allergies and the effect is influenced by multiple causes including prenatal arrangements, perinatal conditions, age, antibiotics. However, still further research is required in the above area to make confirmatory conclusions.

Conflicts of interest
The authors declare no conflicts of interest.

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Cow milk induced allergies (CMA) and asthma in newborn

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