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Cow milk induced allergies (CMA) and asthma in new born

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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 a and allergic diseases. Several studies h plored the associations between perinat tors and children's use of antibiotics and th of asthma, with inconsistent findings.

The present review article will be focused the important findings related ctors re sponsible for above allergic ng with asthma in young infants. , the i ence of cow milk intake will also ken thi unt to cover the aspect of cow ind and asthma in infant

Key Words
Allergy, Infant Genetics, C milk allergy (CMA).

Introductio

gy and hma are the most common ch onditi childhood. The preva- of as ar ergic diseases like allergic rh in chi has shown an increasing trend in s al industr ized countries since the second h eth century[1]. In some countries, the valence is still rising, although in other countries prevalence seems to have declined[2]. The devel- t of asthma and allergic diseases has a strong ge background. The rise in the prevalence of these diseases indicates that environmental factors also play an important role as well[3].

The gut microl a p mport ble in the maturation develo t of mmune system. The ular "mic ypothesis" suggested rbations in gastrointestinal mic ota a ult of reduced microbial exposure result in i re microbiota, which mi y proper ma on of the immune s m, and the resulted delay usually led to an ease in asth and allergic diseases[4]. The rs that have en suggested to be related to t velopmen asthma included infections, non crobes, dietary factors, exposure to smoke, air pollutants and allergens[5]. Also a report in recent past[6] suggested that factors related to pregnancy, delivery and t wth 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 mechanisms[7]. Cow's milk allergy (CMA) is defined

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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[8]. 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'smilk 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[8]. There is a consensus that the diagnosis of food a... has to be based on oral food challenge pro... that establish a causal relation between the ...s-tion of a particular food and a subsequent cli... reaction[9]. Of the different challenge procedu... double-blind placebo-controlled ... challeng... is considered the "golden st... diagnos-ing food allergies. Howev... ly a ...ority of studies related to CMA ...sed th... and, in epidemiologic re... defined as either pa...ly re... or oral food challenge confirm... MA.

Asthma

Asthma ...defined as ...nic inflammatory disorder ...ciated with var... irflow obstruction a... ronchi... hyper-respo...siveness[10]. A key co...ent in... pathology is chronic inflammat... ...ous fac... such as viruses, allergens a... cise. Th... factors also responsible ...per ...si...ess, inflammation together wi... yper-re... associated with airway obstru...n. Asthma can present with symptoms s... nt episodes of wheezing, coughing, shortness of breath, and chest tightness. In ...idemiological research, according to Spycher et ...ost 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 ... wheeze and asthma). In children, th... urren... of recurrent wheezing episodes i... universally accepted starting point of asthm... gnosis. In addition to medical history, metho... tablish asthma diagnosis include ...ical exa... ion evaluation of lung fun..., atopy, airw... flammation, bronchial ...er res... iveness ... exclusion of alternat... agnos... in you... children, the asthma ...agn... articul... challenging due to ...iculties ...plyi... objective lung function ...surements. ...nfants and preschool-...ren, the di...sis is often based on ...dical ... and symptoms.

The ...of gut Micr...ta in the D...elopment of Asthma and Allergic ...eases

The gut micro...a is a major source of microb... posure, ...aining an assortment of micro-... abiting the entire gastrointestinal trac... ization of the human gut microbiota begins immediately at birth, as upon passage ... the birth canal infants are exposed to a ...mp... 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[12]. 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[13] and tolerance to inhaled aeroallergens[14]. 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[15]. 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[16].

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[17]. 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[18] 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 the... sociations have not been replicated[18]. S... the genes associated with food allergy a... so associated with asthma, although the relev... of these genes to both food allergy and asth... together remains to unexplored.

Environmental Factors ... the ...ergies

The priming of the i... e syste... in early childhood or eve... be... i... as p... ed the idea of a "cri... time ... w" for environmental factors ... ome into p... nd impact the developmen... a and allerg... seases[3]. Knowledge o... role ... fferent environmental factors in ... developme... CMA or any food allergy ... ins limited, bu... e extensive research ... been conducted on the associations bet... diffe... environmental factors and the deve... asthma ... childhood. The factors that ha... n sugg... d to be associated with ...velop... of ... ma included microbial infec... s, dieta... tors, and exposure to tobacco sm... air pollut... nts and allergens[5]. As the moth... e environment for the child for the ... nine months and after birth continues as the ...sest caregiver, she can be considered as a ma... ...ironmental factor operating for the child's dev... pment. Thus, various factors related to prenatal period, i.e. pregnancies as well as deliveries have received growing attention[6].

Infections and non-Pathogenic Microbes Associated with Allergies

Infections in early childhood have been implicated in the development of asthma... their role is complex. For example, ... re low... respiratory tract infections have b... associated with an increased risk of asthma ... repeated viral infections have been r...ported ... asso... ciated with a decreased ri... Further... rect... measures of infections li... e care of a ch... daycare centre and his... mber ... der sibl... have been shown to ... ociat... with bo... a decreased and an in... asc... asthm... . Despite the fact t... evere ... respi... ry tract infections ha... en linked t... velopment of asthma ... unclear wh... r these lower respira... y trac... tions caused subsequent development of asth... whether these infectio... y mark indiv... s that have a genetic ... opensity for developing asthma[19]. Further, ...s been sugg... ed that qualitative aspects of ...tions such a... ming, type and intensity may b... ial in the ...elopment of asthma. There is cur... nce that infections would play a major ... the development of cow's milk allergy or any food allergy in early childhood. Further, ... not only pathogenic microbes causing ... inf... atic infection, but also non-pathogenic microbes have been suggested as playing a role in the development of asthma and allergic diseases. Several studies[24] 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[25]. In addition, an observation that microbial diversity of house dust was inversely related to the prevalence of childhood asthma independently of farming status[26] and that a lower environmental biodiversity in the surroundings of study subjects' homes was more common in atopic than in nonatopic adolescents[27]. 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[28]. 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[29]. Observational studies have reported inverse associations between asthma and n-3 polyunsaturated fatty acids and dietary a... idants in the postnatal diet, although suppl... tion of infants' diet with fish oil or vitamin ... ve so far failed to show any major benefit. A mat... intake of antioxidant rich foods, fish oil and v... min D during pregnancy has be... rted to ... inversely associated with wh... g, ...ma and other allergic diseases in the ...pring. ...ddition, limited intervention data ...sted th... efits of fish oil supple... nta... preg... in reducing the risk ...rgic ... in offspring.

Maternal Fac... Cow's Mi... ergy and Asthm...

Materna... ge at delive... been observed to be inver... associated with ... isk of asthma in two s... es[30,31], ...rectly associated in one study (Jul... al 200... nd not associated in two studies[3... ...die... McKe... et al[33] and Bråbäck et al[34] fou... depen... associations; the inverse ...iation ...tr... er or present in children diag... d with ...a at early ages, whereas the ass... tion was ...eaker or not present in children d... ...der ages.

...vidence on the role of exposure to smoking on ... development of various food allergies is lim... A birth cohort study[35] explored infant feeding ...tterns 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 a... In a study in the recent past[37], an inc... d risk ... asthma was observed in children ...nosed with asthma at early ages, whereas no ...iation was observed in children diagnos...d at o... ...s.

Perinatal Factors

In perinatal factors ... mode ... elivery ... ters to some extent. ... meta... lyses[38,39] have recently summari... th... tion be... n delivery by caesa... section ... the ... of asthma. Both me... alyses conc... t delivery by caesare... was associa... with a roughly 20% in... ase in ... bsequent development of asthma compared wi... inal delivery. In addition, studies have r... ed an increased risk o... thma in children born by assisted vaginal ...very compar... with children born by normal ...taneous va... l delivery[40,41], whereas also n... sociation ... assisted vaginal delivery has bee... ...ted.

Evid... fetal growth and the risk of CMA and other food allergies is limited. Low birth ... has been associated with a decreased risk ... allergy[43], but also no association between low birth weight and/or gestational age has been reported[44]. Liem et al[44] 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[45,46]. A largest cohort study[46] 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[47] the strongest association was observed for macrolides. Also, Stensballe et al[47] 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[48] 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[49,50] 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[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 than in later childhood. Further, an increased risk of asthma has been observed in children diagnosed at early ages, but not in children diagnosed at older ages[53].

Conclusions

So, this can be concluded from the review that external feeding including Cow' milk is o[illegible] of the prominent cause of paediatric allerg[illegible] the effect is influenced by multiple causes i[illegible]d-ing prenatal arrangements, perinatal condit[illegible] age, antibiotics. However, still further researc[illegible] required in the above area to m[illegible]firmato[illegible] conclusions.

Conflicts of interest

The authors declare n[illegible]flicts [illegible]est.

Re[illegible]ces

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