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■ Review article ■

Environmental tobacco smoke and childhood asthma

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= Abstract =

In recent years, environmental tobacco smoke (ETS) has become an important worldwide public health issue. Children are particularly vulnerable to ETS because they are still developing. ETS exposure causes a wide range of adverse health effects on childhood asthma. There is convincing evidence that ETS exposure is causally associated with an increased prevalence of asthma, increased severity of asthma and worsening asthma control in children who already have the disease, even though a causal relationship with asthma onset is not yet established for asthma incidence. Mechanisms underlying these adverse effects of ETS are not clearly elucidated but e studies on this issue suggest that genetic susceptibility, impaired lung function, and augmented airway inflammation and remodeling may be involved. Children with asthma are just as likely to be exposed to ETS as children in general and there is no risk-free level of exposure. Therefore, providing a smoke-free environment may be of particular importance to the asthmatic children exposed to ETS who have adverse asthma outcomes, as well as to children with genetic susceptibility who are at increased risk of developing asthma upon exposure to ETS in early childhood. (Korean J Pediatr 2010;53:121-128)

Key Words : Environmental tobacco smoke, Adverse effect, Asthma, Children, Gene, Lung function, Airway hyperresponsiveness, Inflammation, Remodeling

Introduction

In recent years, environmental tobacco smoke (ETS) has become an important worldwide public health issue. Tobacco smoke is a complex mixture of over 4,000 chemicals, at least 250 of which are known to be human carcinogens, toxic substances, and irritants to the respiratory system[1]. ETS is mainly composed of sidestream smoke from the burning end of cigarettes, with the addition of a smaller amount of exhaled mainstream smoke from the smoker. Although the chemical compositions of sidestream and mainstream smoke are qualitatively similar, sidestream smoke contains greater amounts of certain carcinogens and toxic substances because it is generated at lower temperatures under different conditions[2]. In addition, particles in ETS are more likely to penetrate into the deeper airways due to their smaller size compared with those in mainstream smoke. ETS, therefore, seems to be more harmful than mainstream smoke.

Children are particularly vulnerable to environmental toxicants including ETS. This heightened susceptibility derives primarily from the unique biological features that characterize the various stages of development from conception to adolescence. Developing organisms are more vulnerable to ETS for a variety of reasons including greater and longer exposure and particular susceptibility windows[3].

Although parental smoking is the chief source of ETS exposure for children, as they grow and spend less time with their parents, sources of ETS outside the home may become important. The Global Youth Tobacco Survey (GYTS), of nearly 750,000 students aged 13 to 15 years recruited from 131 countries, found that ETS exposure was high both at home (42.5%) and in public places (55.1 %)[4]. The GYTS data showed that the prevalence of ETS exposure was also high in the Republic of Korea where 39 % of students were exposed to ETS at home, and 65% were exposed to ETS in public places. Children with asthma are just as likely to be exposed to ETS as children in general and there is no risk-free level of exposure[5].

Exposure to ETS causes a wide range of adverse health effects in children. Children exposed to ETS are more susceptible to respiratory tract and middle ear infections.

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Sudden infant death syndrome, behavioral and neurocognitive problems have also been linked to ETS exposure[5].

A large amount of literature also demonstrated the effect of ETS exposure on childhood asthma. Exposure to ETS has been linked to several adverse asthma outcomes including increased prevalence of asthma, increased severity of asthma symptoms, increased frequency of asthma medication use, and increased emergency room visits by asthmatic children[6-8]. Although the results of epidemiological studies of ETS exposure and asthma have predominantly been based on self-reported ETS exposure (with potential recall bias of exposure to ETS), some epidemiological studies have also used personal nicotine monitoring, hair nicotine, and cotinine assays to provide objective measures of ETS exposure. Generally, the results of questionnaires and biochemical assessments were similar[6].

This review focuses on recent evidence for the role of ETS in development of asthma and the effects of ETS on established asthma in children. The potential mechanisms suggested in recent epidemiological and experimental studies are also described.

The role of ETS in development of asthma

There is convincing evidence from case-control studies that parental smoking is causally associated with an increased prevalence of asthma. Cook and Strachan[9] performed a meta-analysis of 25 studies to assess the effects of parental smoking on the prevalence of asthma and found that the pooled odd ratio (OR) for either parent smoking was 1.21 [95% confidence interval (CI) 1.17-1.31] with very little effect of adjustment. A more recent meta-analysis of 41 relevant studies performed by the US Surgeon General also concluded that the evidence was sufficient to infer a causal relationship between parental smoking and ever having asthma among children of school age with the pooled OR of 1.23 (95% CI 1.14-1.33)[6].

In contrast to the prevalence of asthma, the evidence form cohort studies indicating an association of ETS exposure from parental smoking with incidence of asthma is inconsistent. A cohort study in Finland followed 2,531 children from birth through age 4 and found that ETS exposure at birth was associated with a greater risk of bronchial obstruction during the first 2 years of life (OR 1.43; 95% CI 1.07-1.90). However, the relation between ETS exposure and asthma at 4 years of age was less clear (OR 1.10; 95% CI 0.79-1.53)[10]. In a birth cohort study of 762 children in Tucson, 3 wheezing phenotypes in the first 6 years of life were identified; transient early wheezing (wheezing by 3 years of age but not at 6 years of age), late-onset wheezing (wheezing after 3 years of age), persistent wheezing (wheezing before 3 years of age and continued wheezing at 6 years of age). Maternal smoking was associated with increased incidence of wheezing before 3 years of age, but not late-onset wheezing[11]. In quantitative meta-analyses of 8 cohort studies, the association with ETS exposure from parental smoking was significantly stronger for the first 5 to 7 years of life than for the school years or throughout childhood excluding infancy with the pool OR of 1.31 (95% CI 1.22-1.41) and 1.13 (95% CI 1.04-1.22), respectively[8]. The 2006 Surgeon General's report examined the association between ETS exposure and incidence of asthma and wheeze illnesses and concluded that the evidence was sufficient to infer a causal relationship between ETS exposure from parental smoking and the onset of wheeze illnesses in early childhood, but not sufficient between ETS exposure from parental smoking and the onset of childhood asthma[6]. On the other hand, the California Environmental Protection Agency (CEPA) conducted a meta-analysis of 37 studies that evaluated the impact of ETS exposure on induction of childhood asthma and concluded that while preschool children appeared to be more at risk than older children, older children exposed to ETS were also at significant risk for new onset asthma (OR 1.26; 95% CI 1.19-1.32)[12]. Overall, considering various wheezing phenotypes in children, studies on incidence of asthma suggest that parental smoking, particularly maternal smoking, is associated with increased incidence of early wheezing, whereas the incidence of asthma during school-age years is less strongly affected by parental smoking.

The influence of various factors on association between ETS exposure and the development of asthma has been investigated. Martinez et al.[13] conducted a case-control study of more than 700 children in Tucson and found that children were 1.6 times more likely to develop asthma if their mother smoked 10 or more cigarettes per day (95% CI 1.10-2.58). Similar observations were reported in other studies where maternal smoking of more than half a pack of cigarettes per day was an independent risk factor for childhood asthma[14-16]. These results suggest that a threshold of ETS exposure intensity is required to make the

response.

The role of atopy in the association between ETS exposure and development of asthma is contradictory. In a British cohort study, maternal smoking during pregnancy was associated with an increased risk of childhood wheezing among non-atopic subjects but a slightly decreased risk among atopic subjects[17]. A Canadian cross sectional study of 892 subjects age 6-17 years also reported similar result[18]. However, another Canadian cross sectional study reached opposite conclusion. Children with atopic dermatitis had increased risk of developing asthma if their mothers were smokers (OR 3.42; 95% CI 1.60-7.30), whereas children without atopic dermatitis had similar risk regardless of maternal smoking status (OR 0.93; 95% CI 0.57-1.51)[19].

The timing of ETS exposure in the development of asthma also remains under debate. Because most smoking mothers never change their smoking habits after delivery, it is difficult to separate the effect of prenatal ETS exposure from that of postnatal ETS exposure. A Finnish cohort study of 58,841 children found that maternal smoking during pregnancy increased the risk of asthma during the first 7 years of life (OR 1.35; 95% CI 1.13-1.62)[16]. In another study of 705 fifth grade students, maternal smoking during pregnancy rather than current smoking was associated with asthma[20]. The association between maternal smoking during pregnancy and asthma has been supported in several other studies[15, 21, 22]. In addition, maternal exposure to ETS during pregnancy is also associated with increased prevalence of childhood asthma[23, 24]. However, other studies on this issue have shown conflicting results [25, 26]. In a Norwegian study of 620 children aged 7-13 years, postnatal smoking by the mother was more strongly related to asthma compared with prenatal smoking (OR 2.8; 95% CI 1.3-6.1)[26]. Although the effect of maternal smoking is greater than that of paternal smoking, there is evidence of a small independent effect of paternal smoking[12, 27, 28]. These results also suggest a role for postnatal secondhand smoke exposure.

The effect of ETS on established childhood asthma

ETS exposure has been linked to worsening established asthma in children. A cross-sectional study of 523 children with physician-diagnosed asthma examined the impact of ETS exposure on asthma severity. Asthmatic children with high levels of smoke exposure were more likely to have moderate or severe asthma compared with those with low levels of exposure (OR 2.7; 95% CI 1.1-6.8)[7]. The relative risk for acute exacerbations of asthma in the previous year in the highest level of urine cotinine as compared with the lowest was 1.7 (95 CI 1.4-2.1)[29]. A 3-year prospective cohort study of 167 children aged 6-12 years with mild or moderate persistent asthma found that maternal smoking within the home was inversely associated with asthma symptom control (OR 0.34; 95% CI 0.14-0.89)[30]. In a US cohort study of 1,932 fourth-grade children, the risk of school absenteeism for respiratory-related illness among asthmatic children exposed to 2 or more smokers was 2.55 (95% CI 1.78-3.65) compared with not exposed to ETS (RR 1.48; 95% CI 1.17-1.81)[31]. In a qualitative review of 13 studies on asthma severity in relation to parental smoking, ETS exposure increased disease severity including symptom scores, attack frequency, medication use, hospital attendance, and life threatening bronchospasm in children with asthma[8]. Recently, through a systematic review of additional newer studies of asthmatic children exposed to ETS, the Surgeon General's report and the California Environmental Protection Agency review affirmed the finding of previous reviews and concluded that ETS exposure was a causal factor in worsening existing asthma[6, 12].

Inhaled corticosteroid (ICS) therapy is the cornerstone of asthma management. Smoking significantly reduces the efficacy of ICSs[32-34], as well as oral corticosteroids[35] in asthmatics. In a double blind placebo-controlled study of ICSs in mild asthmatics, nonsmoking asthmatics had significant improvements in forced expiratory volume in one second (FEV1), airway hyperresponsiveness (AHR), and sputum eosinophils, whereas smoking asthmatics did not have any of these improvements with ICS therapy[32]. A British multicenter study compared low-dose vs. high-dose ICSs in mild asthmatics[34]. Among those receiving low-dose ICSs daily there was a difference in the mean morning peak expiratory flow rate (PEFR) and in the number of asthma exacerbations between smokers and non-smokers. In contrast to the difference in response to the low dose of ICSs, these differences were reduced between smokers and non-smokers receiving high-dose ICSs daily. In a placebo-controlled, crossover study with prednisolone in asthmatics, there was a significant improvement after oral prednisolone in lung function (FEV1, morning PEFR) and asthma control score in never-smoking asthmatics, but no change in smoking asthmatics[35]. Thus, smoking also

impairs the efficacy of short-term oral corticosteroid treatment in chronic asthma. Overall, results from several studies of ICSs and oral corticosteroids in asthma suggest that smoking asthmatics have a significantly reduced therapeutic response to corticosteroids compared with nonsmoking asthmatics.

However, there is no current information as to whether significantly lower levels of tobacco smoke exposure from ETS might also impair the corticosteroid response in asthmatics who do not smoke but are exposed to ETS. In an animal model of chronic ETS exposure to assess the efficacy of corticosteroid in mice exposed to the combination of chronic ETS and allergen, exposure to low levels of tobacco smoke in ETS did not impair the ability of corticosteroids to reduce airway inflammation, mucus expression, airway remodeling, and AHR[36]. However, as with all studies in animal models, further human studies are needed to determine whether similar results would be observed in asthmatics exposed to ETS who are treated with low or high doses of ICSs.

Taken as a whole, there is now sufficient evidence to conclude that ETS exposure is causally associated with increased severity of asthma and worsening asthma control in children who already have the disease.

Potential mechanism underlying the effect of ETS on asthma

1. Genetic susceptibility

Asthma has a multifactorial cause involving both genetic and environmental factors. Recent studies suggest that specific genes may exist that increase the susceptibility to develop asthma in the presence of ETS exposure. Glutathione S transferase (GST) M1, which is involved in detoxification of both reactive tobacco metabolic intermediates and reactive oxygen species, has been linked to ETS exposure and increased risk of developing asthma in children[37, 38]. A large population of 3,054 schoolchildren aged 9-11 years in Germany was genotyped to assess the effect of deficiencies of GST M1 and ETS exposure on childhood asthma. The GST M1 null children who were exposed to current ETS had an increased risk for current asthma (OR 5.5; 95% CI 1.6-18.6) compared with GST M1 positive individuals without ETS exposure[38].

Recently, a genomewide association study has shown an association between variants at chromosome 17q21 and an increased risk of asthma[39, 40]. A French study of 1,511 subjects from 372 families showed an increased risk of early-onset asthma conferred by 17q21 genetic variants which was further increased by early-life exposure to ETS[40]. Other linkage studies, which have stratified asthmatics based on ETS exposure, have demonstrated that certain chromosomal regions which show strong linkage with asthma and AHR (e.g., 1p, 3p, 5q, 9q) may harbor genes that exert their effects mainly in combination with ETS exposure[41, 42].

In a case-control study of 900 children in the US, Grandmaternal smoking during the mother's fetal period was associated with increased asthma risk in her grandchildren (OR 2.1; 95% CI 1.4-3.2)[43]. This observation raised the possibility that epigenetic mechanisms may be involved in the inheritance of asthma susceptibility. Thus, a gene environment interaction between ETS exposure and a genetic susceptibility may be causally involved in the development of asthma in some, but not all, children with asthma.

2. Lung function and airway hyperresponsiveness

In 1986, the US Surgeon General reviewed 18 cross-sectional and longitudinal studies and first reported that maternal smoking reduced lung function in young children[44]. Since then many studies have reported similar findings and the weight of evidence has been sufficient to conclude that prenatal and/or postnatal ETS exposure adversely affects the lung function of children. Cook and colleagues[45] performed a meta-analysis of 21 studies and concluded that maternal smoking is associated with small but statistically significant deficits in FEV1 and other spirometric indices in school aged children. The percentage reduction in FEV1 in children exposed to parental smoking was 1.4% when compared with those not exposed. Effects were greater on mid expiratory flow rates (-5.0%) and end expiratory flow rates (-4.3%). Much of the effect may be due to maternal smoking during pregnancy. Maternal smoking affects lung development in utero perhaps by a direct toxic effect, by gene regulation, or by leading to developmental abnormalities.

Airway hyperresponsiveness (AHR) is the cardinal feature of asthma although it is also demonstrable in conditions other than asthma. Several studies suggest a relationship between ETS exposure and development of AHR. Airway responsiveness was increased in infants with a family his-

tory of asthma and/or parental smoking as compared with infants with no family history of asthma or smoking[46]. The concentration of histamine causing a 40% fall in lung function indices from baseline value (PC_{40}) were measured in 63 normal infants at a mean age of 4 1/2 weeks to assess the effect of ETS exposure on airway responsiveness. PC_{40} was higher in infants with no family history of asthma or parental smoking than in infants with a family history of asthma and/or parental smoking. In meta-analysis of 10 studies on the effect of ETS exposure on AHR, a small but real increase in airway responsiveness amongst the children exposed to maternal smoking was suggested (OR 1.29, 95% CI 1.10 to 1.50)[47]. The conclusion is not definitive due to limited data included in the meta-analysis.

In a cross-sectional study of asthmatic children exposed to ETS, the ETS-exposed children had greater AHR, as indicated by a lower dose of inhaled carbachol that doubled specific airway resistance (SRaw) and enhanced bronchodilator response[48]. In addition to epidemiological studies, experimental ETS challenge studies in humans indicate that ETS exposure has adverse effects on airflow and/or airway responsiveness in asthma[49, 50]. A significant percentage of smoke-sensitive asthmatics challenged on one occasion with ETS for 4 hours developed increased airway responsiveness to Methacholine (Mch). Acute ETS exposure increased airway responsiveness in 32% of smoke-sensitive asthmatics at 6 hours, 29% at 24 hours, and the increased airway responsiveness was sustained in up to 13% of asthmatics to day 14 after ETS challenge[49].

In an animal model of asthma, the combination of chronic ETS and allergen co-exposure significantly increased airway responsiveness in mice compared with chronic exposure to either stimulus alone[51]. The increased thickness of the peribronchial smooth muscle layer in mice co-exposed to chronic ETS and allergen was associated with a significant increase in airway responsiveness to Mch. Exposure of mice to chronic ETS alone did not induce a change in AHR to Mch. If exposure to ETS and allergen in humans with asthma also induces increased thickness of the smooth muscle layer and increased airway responsiveness as noted in this mouse study, this could provide a potential explanation for the increased frequency of asthma exacerbations, and emergency room visits in asthmatic children whose parents smoke.

Overall, the current evidence relating ETS exposure to the development of AHR is suggestive but not sufficient. It is unclear whether ETS exposure is causally related or it only unmasks and aggravates pre-existing AHR. As such, the effect of ETS exposure on AHR may be only one of the possible mechanisms involved in the induction of asthma.

3. Allergic inflammation and remodeling

Asthma is a disease associated with airway inflammation. Proinflammatory cytokines derived from Th2 lymphocytes, such as IL-4, IL-5, and IL-13, play an important role in inflammatory processes in the airways. The over-expression of these cytokines results in the recruitment and activation of a wide variety of effector cells.

In a study of 24 atopic children with asthma and 26 healthy control subjects, IL-13 secretion in nasopharyngeal aspirate was significantly increased in children exposed to ETS at home compared with non-exposed children and healthy control subjects[52]. An experimental ETS challenge study in humans has provided further evidence that ETS and allergen can interact to exacerbate allergic responses. In a placebo-controlled crossover study, 19 nonsmoking volunteers with ragweed allergy were exposed to ETS in a chamber for 2 hours and then received a nasal challenge with ragweed allergen. Four days after exposure to ETS and ragweed, allergen-specific IgE levels in nasal lavage were on average 16.6-fold higher than after clean air and ragweed challenge. There was an increase in Th2-cytokine (IL-4, IL-5, and IL-13) levels in nasal lavage and a decrease in interferon (IFN)-γ level after ETS and ragweed challenge compared with clean air and ragweed challenge. However, ETS exposure alone did not significantly enhance IL-4, IL-5, IL-13, or IFN-γ responses in lavages[53].

Several animal studies examining the effect of ETS exposure in combination with allergen exposure have demonstrated enhanced Th2 responses and supported the observation in the human study[54, 55]. However, other studies have demonstrated that the combination of ETS and allergen exposure can inhibit Th2 responses and AHR[56, 57]. The differences in the results in these studies may be due to differences in ETS and allergen exposure protocols, differences in exposure to mainstream smoke vs. ETS, as well as differences in timing of ETS exposure during sensitization compared with the allergen challenge period.

Recently, the effect of ETS on angiogenesis and leukocyte recruitment, both of which promote lung inflammation, was investigated in murine model. Mice exposed to ETS for 12 weeks exhibited significantly increased vascular density

and increased intravascular leukocyte rolling and adhesion in the lung[58]. This ETS-induced angiogenesis and leukocyte trafficking can be associated with augmented airway recruitment of inflammatory cells in asthma.

Epidemiological studies in asthma demonstrate that asthmatics who smoke have a greater decline in FEV1 when followed over a 15-year period compared with asthmatics who do not smoke, suggesting that tobacco smoke may contribute to the decline in lung function and airway remodeling[59]. Because of the difficulty in obtaining airway tissue from children, limited information is available on the effects of ETS exposure on the structure of their airway wall. In a postmortem study of SIDS, airway wall thickness was greater in the larger airways of infants exposed to a high level of ETS[60]. Thickened airways could have major effects on airway physiology and explain the increased airway reactivity in infants with a history of exposure to maternal smoking.

No studies have directly assessed levels of airway remodeling in asthmatics exposed to ETS to determine whether ETS exposure is associated with increased levels of airway remodeling. In a well-defined murine model of chronic ETS exposure, chronic co-exposure to the combination of ETS and allergen induced significantly increased levels of peribronchial fibrosis, increased thickening of the smooth muscle layer, increased mucus, and increased airway responsiveness compared with levels of airway remodeling noted in mice from chronic exposure to either stimulus alone. However, mice exposed to chronic ETS alone did not develop significant eosinophilic airway inflammation and airway remodeling[51].

Conclusion

ETS Exposure causes a wide range of adverse health effects on childhood asthma. There is convincing evidence that ETS exposure is causally associated with increased prevalence of asthma, increased severity of asthma and worsening asthma control in children who already have the disease, even though a causal relationship with asthma onset is not yet established for asthma incidence. Mechanisms underlying these adverse health effects of ETS are not clearly elucidated but e studies on this issue suggest that genetic susceptibility, impaired lung function, and augmented airway inflammation and remodeling may be involved. There is no risk-free level of exposure to ETS. Therefore, providing a smoke-free environment may be of particular importance to the large number of asthmatic children exposed to ETS who have adverse asthma outcomes, as well as to children with genetic susceptibility who are at increased risk of developing asthma on exposure to ETS in early childhood.

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