REVIEW

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Allergic rhinitis: Aetiology, predisposing and risk factors*

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SUMMARY

The reason for examining the predisposing and risk factors that affect the prevalence of allergic rhinitis is to help understand its cause and prevent its occurrence particularly in the light of the marked increase that is taking place in the prevalence of this condition. The epidemiology in different population groups and studying patient's family histories may give us clues about what factors predispose people to developing allergic rhinitis. Furthermore we can gain a better understanding of the disease mechanisms from the histological and molecular tissue studies that relate to allergic rhinitis.

Key words: allergy, rhinitis, aetiology, predisposing factors, nasal

INTRODUCTION

It has been suggested that there is a balance in an individual's helper T cell response between TH1 cells and TH2 cells (Berger, 2000). TH1 cells produce cytokines that produce the pro-inflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses. TH2 cells produce cytokines associated with the promotion of IgE and the eosinophilic responses in atopy. It has been suggested that in allergic rhinitis and seasonal asthma, an individual with a genetic predisposition towards a TH2 biased immune system could move away from this bias if exposed to certain environmental stimuli early in life (Openshaw, 1999; Openshaw and Hewitt, 2000). Early exposure to microbial agents may be the appropriate stimulus causing the immune system in these individuals to move towards a TH1 dependent system (Strachan et al., 2000). Strachan described the "hygiene hypothesis" and suggested that larger households predispose to infection in early childhood transmitted by contact with older siblings, and through this a down-regulation of the TH2 response that confers a protective effect (Stachan et al., 2000). It has been suggested that there is a balance in an individual's helper T cell response between favoring Th1 cells or Th2 cells (Berger, 2000). Th1 cells produce cytokines which produce the pro-inflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses. Th2 cells produce cytokines which are associated with the promotion of IgE and eosinophilic responses in atopy. It has been suggested that in asthma an individual with a genetic predisposition towards a Th2 biaed (i.e. atopic) immune system could move away from this bias if exposed to certain environmental stimuli early in life (Openshaw and Walzl, 1999). Without this biological programming the bias would persist and the individual would tend towards a Th2 dependent system, i.e. atopy.

Family history and Genetics

A family history of allergic disorders is strongly associated with the development of allergic rhinitis in most studies (Sibbald and Rink, 1991; Bahana, 1992; Wright et al. 1994), and is reported in up to 56.6% (Van Arsdel and Motulsky, 1959). Segregation analysis has suggested that genes influence atopy and IgE levels and one of the first linkages found was to chromosome 11q13 (Cookson et al., 1989). Recently several more potential linkages have been identified (Daniels et al., 1996). Three of these loci demonstrate linkage to a second panel of families in which maternal effects and pleiotropy, when a single gene can affect two or more characteristics, have been found. This shows the complex relationship of genes and the asthma phenotype. Essentially, two classes of genes influence specific IgE reactions; HLA protein genes and T cell receptor genes (Moffat et al., 1994a). These genes influence the response to specific antigens, the intensity of any reaction, the level of IgE production, and other alleles may influence the secretion of tumour necrosis factor α and affect the inflammatory reaction.

In allergic rhinitis there is good epidemiological and basic scientific evidence that the genes that are responsible are inherited (Moffat et al., 1994b). However, why 15.5% of asymptomatic people who have a positive skin prick test do not develop allergic symptoms (Droste et al., 1996) and only 35% of those with a raised IgE have symptoms of rhinitis is unclear (Panzani et al., 1993). Kelso (Kelso, 1996) found that first degree relatives with allergic rhinitis are no more statistically significantly likely

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to be skin test positive to the same allergens than unrelated persons with the positive concordance rate was 30% in related, and 21% in unrelated people. In another study, the skin prick tests of 18% of children changed over 2 a year period demonstrating that the markers of atopy are not static (Droste et al., 1996). An understanding of the normal course of these processes may help us to learn how we might influence our immune status and suppress the excessive responses to foreign antigens that lead to the symptoms of allergic rhinitis.

There are conflicting studies about the genetics of atopy reporting that atopy is transmitted through a single recessive autosomal gene (Gerrard et al., 1978), or through maternal chromosomes (Cookson and Hopkin, 1988). Others suggest that atopy is linked to a number of candidate chromosomes associated with features linked with atopy such as bronchial hypereactivity (chromosome 6), total serum IgE and eosinophilia (chromosome 6), bronchial hypereactivity, total serum IgE and eosinophilia (chromosome 7 and 16), total serum IgE, positive skin prick tests and asthma (chromosome 11), atopy (chromosome 13) (Daniels et al., 1996).

Birth order, family size and number of upper respiratory tract infections

Strachan (Strachan, 1989; Strachan, 1995) showed that the prevalence of hay fever is reduced in those with more siblings, but not in households with crowding and more than 1 person per room. Golding and Peters (Golding and Peters, 1986) studied a cohort of children born in 1970 and found that in 5 year olds, 6% of single children had hay fever compared with 1.3% of children with more than 4 siblings. Taylor et al. (Taylor et al., 1983) and Butland et al. (Butland et al., 1997) reported a higher prevalence of hay fever in firstborn children. Crane et al. (Crane et al., 1994) also found that the risk of developing atopy is higher for children in small families. A trend in many countries for smaller families was postulated as a possible factor for the apparent increase in prevalence of allergic diseases. This led to the hypothesis that infections in childhood had a protective effect by upregulating the TH1 lymphocyte system. Other studies have reproduced the finding that hay fever is reduced in those with more siblings (McKeever et al., 2001; Marshall et al., 2002). Svanes et al. found a protective effect against atopy in siblings with no parental history of atopy as well as sharing a bedroom as a child, no matter the number of siblings (Svanes et al., 1999). The evidence as to whether a child entering day nursery from an early age, and thereby being at an increased risk of developing more infections, has been contradictory with some showing it confers a reduced risk (Kramer et al., 1999), whilst others have shown the opposite (Kipelainen et al., 2000). Wickens et al. reported that the changes in family size over the past 30 years do not appear to explain much of the reported increase in the prevalence of asthma and hay fever (Wickens et al., 1999). A recent review on the subject by the worker who first found an association between an increased family size and a reduction in the incidence of atopy says "… infections remain the most promising candidates for the underlying protective factor" (Strachan, 2000). McKeever et al. found a dose-related decrease in the incidence of hay fever with increasing numbers of siblings (McKeever et al., 2001). However, the same group found no evidence that exposure to infections reduced the incidence of allergic disease and infections did not explain the previous findings of a strong birth order effect in the same study cohort (McKeever et al., 2002).

Von Mutius et al. (von Mutius et al., 1992; Von Mutius et al, 1994) postulated that repeated respiratory tract infections in childhood encourages the maturation of T-helper cell response to inhaled allergens and this inhibits the development of allergic rhinitis. Shaheen (Shaheen, 1994) suggested that not only does a reduction in the infant infection rate relate to an increase in allergic disease but that the age of infection, the type of organism and its virulence may influence allergic sensitization.

A study by Paunio et al. suggested that becoming infected with measles has a protective effect (Paunio et al., 2000) but this study has been criticised for not accounting for many in the study having already received measles vaccination (Gern and Weiss, 2000). Support is provided by other studies that measles has a protective effect (Shaheen et al., 1996a; Shaheen et al., 1996; Lewis and Britton, 1998) although a study of a British cohort, half of whom had undergone measles immunisation, found no substantial difference in the prevalence of hay fever (Golding and Peters, 1986).

Whole cell pertussis vaccine has been associated with a relative reduction in the risk of developing atopic disease of 8% compared to 10% relative increase with the acellular vaccine (Nilsson et al., 1998). Other studies have suggested that hepatitis A infection also has a protective effect (Matricardi et al., 1999; Matricardi et al., 2000) whilst others have shown mycobacteria to be beneficial (Shirakawa et al., 1997; von Hertzen et al., 1999) but not BCG vaccination (Alm and Lilja, 1997; Strannegard et al., 1998). In adults BCG vaccination had no effect on skin prick tests response to common inhaled allergens or IgE levels (Omenaas et al., 2000). Contrary to these reports, other studies have shown that early infection has no protective effect (Strachan et al., 1996; Bodner et al., 1998; Farooqi and Hopkin, 1998; Alm et al., 1999; von Mutius et al, 1999).

Antibiotic usage in early childhood

McKeever et al. found that antibiotic exposure was associated with an increased risk of developing allergic disease in a dose-related manner (McKeever et al., 2002). Having 4 or more courses of antibiotics in the first year of life was associated with an increased risk of hayfever (hazard ratio 1.14, confidence interval 0.88-1.47) (Farooqi and Hopkin, 1998; Alm et al., 1999; von Mutius et al., 1999; Wickens et al., 1999; Droste et al., 2000). One hypothesis is that antibiotics alter the bacteri-

al flora in the gastrointestinal tract and this reduces the antigenic stimulation that the immune system receives at an important stage in the development of the immune system. However, this association might be explained by the possibility that children who are atopic are more likely to wheeze and receive antibiotics for a chest infection in childhood.

Early allergen exposure

Sporik et al. (Sporik et al., 1990) showed an association in children between high mite allergen exposure before the age of 1 year and the development of asthma at the age of 11. Kramer and Moroz (Kramer and Moroz, 1981) found that infants who were breastfed and had a delayed introduction to solids were less prone to become atopic. Saarinen et al. (Saarinen et al., 1979) provided supporting evidence, showing that a longer period of breastfeeding protected against developing atopy. Contrary to these reports, Butland et al. (Butland et al., 1997) found that those who had been breast fed for more than one month were more likely to develop hay fever.

Exposure to pet allergen

Exposure to dog allergen in childhood has been reported as being associated with a reduction in atopy although this has not been found in cats (Svanes et al., 1999).

Affluence

Min et al. (Min et al., 1997) found no differences between different occupations but those with a higher educational attainment had a higher prevalence of persistent allergic rhinitis. Non-manual workers were reported to have higher rates than manual workers in the study based on the Third National Survey on Morbidity Statistics in General Practice (Royal College of General Practitioners, 1986). This may be in part due to doctors being more ready to diagnose hay fever in more privileged social classes, as these findings are reported even when there are no differences between their symptoms or positive skin prick tests (Sibbald and Rink, 1991a). However, many studies have found an association between affluence and allergic disease (Broder et al., 1974; Broder et al., 1974; Gergen et al., 1987; Strachan, 1995).

Geography

Whilst one study showed rhinitis to be more prevalent in dry areas of Australia when compared to temperate areas (Sibbald and Rink, 1991a), this has not been repeated in other studies.

Month of birth

One hypothesis proposed that antigen exposure in the first months of life increase the risk of allergy later in life and that this may prime the immune system. A higher prevalence of allergic rhinitis has been found in children born in the spring or summer months (Morrison-Smith and Springett, 1979; Korsgaard and Dahl, 1983; Aberg, 1989; Pearson et al., 1997) if its onset was before 20 years old (Sibbald and Rink, 1990). However, in Sweden, Norrman et al. (Norrman et al., 1994) reported a higher risk of asthma in teenagers born in winter.

Age

The prevalence of rhinosinusitis varies with age, and attendance's with a primary care physician peak between 5 and 24 years (Royal College of General Practitioners, 1986) Fleming et al. (Fleming and Crombie, 1987) report peak attendance rates as being at the upper end of this range at 15-25 years. Other reports have similar peak prevalence, being 10-19 years in Denmark (Pedersen and weeke, 1981), 16-20 in Japan (Ogino et al., 1990), 24 years in the USA (Broder, 1974), and 25-35 year olds in Australia (Australian Bureau of Statistics, 1991). Richards et al. (Richards et al., 1992) found little difference between the decades from 15-44 but found a fall off after 45 years. Binder et al. (Binder et al., 1982) found hay fever was unusual after 60 years. Wright et al. (Wright et al., 1994) in a USA survey of 747 children aged 6, found 42% had allergic rhinitis diagnosed by a physician, whereas in Korea the prevalence was 1.1% (Min et al., 1997).

As the prevalence of allergic rhinitis decreases over 45 years old it is important to examine the age distribution when comparing populations or the same population over time, particularly as many western populations have a progressive increase in the proportion of elderly people with time. It is interesting that while allergic rhinitis becomes less prevalent with ageing, nasal polyps become more prevalent (Settipane and Chafee, 1977). Approximately 0.5-4.5% of those with allergic rhinitis have nasal polyps (Caplin et al., 1971; Bunnag et al., 1983; Zeitz, 1988; Settipane and Chaffee, 1997) which compares to the normal population (Drake-Lee, 1999). In children the prevalence of nasal polyposis has been reported as 0.1% (Settipane and Chaffe, 1976). Whilst the histopathology of the inflammatory process in nasal polyps appears similar to that in asthma, far from all asthmatics, particularly those with late onset asthma, are atopic or have the markers of a positive skin prick test or raised specific IgE (Harlin et al., 1988).

Changes in the prevalence of seasonal allergic rhinitis

Accurate records of the prevalence of allergic rhinitis are lacking before this century but reports by Bostock (Bostock, 1819) and Elliotson (Elliotson 1830) suggest that it was rare in the early 1800's. There is evidence that the prevalence of intermittent allergic rhinitis and asthma is increasing in Western Europe (Jones et al., 1998). It is important to compare like with like and therefore time interval studies done by the same workers are likely to be more accurate at reflecting any change in prevalence. Finn (Finn, 1992) and Emanuel (Emanuel, 1988) have drawn attention to the fact that there are few reports of allergic rhinitis before the industrial revolution, although this may be due to reduced awareness. In the USA, several studies suggest an increase in the prevalence of allergic rhinitis in college students over the last 70 years (Hagy and Settipane, 1969). The number of primary physician attendencies per 1000 of the

population for seasonal allergic rhinitis increased with each national UK study up to the 1980's (General Registry Office, 1958; Royal College of General Practitioners, 1974; Royal College of General Practitioners, 1986) from 11 in 1971 to 19.7 in 1981. However, Ross and Fleming (Ross and Fleming, 1994), based on the Royal College of General Practitioners weekly returns (1981-92) found no evidence of an increase in the prevalence of allergic rhinitis in the following decade.

The prevalence of persistent allergic rhinitis

The prevalence of persistent allergic rhinitis varies from population to population, being 1.14% in Southern Korea, 2.60% in Northern Korea (Min et al., 1997), 5.2% in the USA (Hagy and Settipane, 1998) 8% in Sweden (Hattevig and Kjellman, 1990) and 12.7% in the Netherlands (Droste et al., 1996). The prevalence of persistent allergic rhinitis in a British population has been reported as 13% in one study (Sibbald and Rink, 1991). The peak prevalence is at 10-19 years (Viner and Jackman, 1976). The study by Min et al. (Min et al., 1997) suggested that age, birth place, current residence and crowding influenced the prevalence of persistent allergic rhinitis. Marital status, employment, smoking, and body weight showed no correlation. However, they listed 17 correlations which suggest that there is the possibility that there was inadvertent "fishing" for a statistically significant result. Each correlation therefore requires further investigation in its own right before any conclusion can be drawn.

Allergy and pollution

The nose filters about 7000 litres of air a day and therefore in vitro studies may not accurately reflect the changes which may occur in a longer period of time with more moderate levels of pollutants. Epidemiological studies are therefore particularly relevant, but controlling for other variables is difficult.

Environmental factors such as pollution and exposure to house dust mite have been implicated as being responsible for the increase in symptoms of rhinitis (Holt, 1996), but the epidemiological evidence to support this is limited (Durham et al., 1997) (Committee on the medical effects of air pollutants, 1995). Gniazdowska and Jemow (Gniazdowska and Jemow, 1990) and Antova (Antova, 1993) have reported that those living in an urban area have a higher prevalence of allergic rhinitis and asthma. A review by Krishna et al. concluded that there is possibly a link between ozone pollution and allergic airway disease (Krishna et al., 1995). Ishizaki et al. (Ishizaki et al., 1987) found that near motorways the prevalence of allergy to cedar pollen was 13.2%, whereas it was 8.8% in the city and farming areas, and 5.1% in an area away from cars but where the pollen count was the same, and 1.7% in the mountains without cedar trees or cars. Weiland et al. (Weiland at al., 1994) in a questionnaire of 2,050 schoolchildren about the prevalence of allergic rhinitis and traffic density showed an increase in prevalence (21.4% to 27.1%) where there was more dense traffic. The adjusted odds ratio for sex, age, number of siblings amongst other variables was 1.36 for high traffic, (95% confidence interval 1.05-1.77). Ross and Flemming (Ross and Fleming, 1994) found that the prevalence of hay fever fluctuated from year to year, coincided with a high pollen count, and was slightly higher in urban areas. Goh et al. (Goh et al., 1986) studying Singapore schoolchildren suggested that there was a connection between sinusitis in children living in an industrial area and levels of SO_2. Suonpaa and Antila (Suonpaa and Antila, 1990) reported a threefold increase in admissions for acute frontal sinusitis over a 5 year period in a town in Finland and attributed it to pollution but without any other data to support this hypothesis. However, Ross and Fleming (Ross and Fleming, 1994) found a similar prevalence of allergic rhinitis throughout England and Wales in 1981-92 with no evidence that pollution had any effect as the size and timing of peak levels were similar in all regions. They added a proviso that although their study suggested pollution had no effect locally, it was nevertheless possible that pollution levels were high enough across the whole country to have a country-wide effect.

Von Mutius et al. (von Mutius et al., 1992) compared the prevalence of allergic disorders between Munich in West Germany and Leipsig in East Germany, the latter having particularly high concentrations of SO_2 and pariculates. They found that in schoolchildren aged 9-11 there was significantly less rhinitis ($p<0.005$) in the more polluted city. Geller-Bernstein and Klein et al. (Geller-Bernstein and Levin, 1987) (Klein et al., 1992) found no difference in the time of onset of intermittent allergic rhinitis in children in an urban area of Israel compared to a rural area. Charpin et al. (Charpin et al., 1988) found no difference in the prevalence of allergic rhinitis in rural and urban areas in France. They found amongst a cohort of 12,355 individuals aged 23, that the prevalence of intermittent allergic rhinitis related more to their region of birth than where they were currently living but that there was no clear rural/urban variation. Studies on skin prick testing have not shown any differences in sensitivity between urban and rural populations (Zwick et al., 1991). Whether the increased prevalence of allergic rhinitis in urban areas found in some studies is due to pollution, a higher level of house dust mite or other factors is not clear (Min et al., 1982). Zwick et al. (Zwick, 1991) (Popp et al., 1989) found an increase in sensitisation to airborne allergens in polluted areas. Dowse et al. (Dowse et al., 1985) produced evidence suggesting that an increase in the prevalence of asthma in Papua New Guinea was due to an increase in house dust mite allergen. Samir et al. (Samir et al., 1997) reported higher cadmium levels in 30 patients with allergic rhinitis compared with a nonallergic rhinitic and a control group. They implied that higher levels of cadmium reflected an increase in exposure to polluted air but the method of this study is not appropriate to demonstrate any causal link. The worldwide International Study of Asthma and Allergies in Childhood (The International Study of Asthma

and Allergies in Childhood (ISAAC) Steering Committee, 1998) found that in regions with the highest levels of particulate and sulphur dioxide pollution there were generally low rates of asthma and allergic rhinoconjunctivitis whereas in areas with high ozone there were intermediate levels of prevalence and in some areas with minimal pollution the prevalence were high. A report on air pollution and allergic disease (Working Party of the British Society for Allergy and Clinical Immunology, 1995) concluded that it is still unclear the extent to which the prevalence of atopy is related to the concentrations of air pollutants.

Trevino (Trevino, 1996) and Albright and Goldstein (Albright and Goldstein, 1996) have suggested that pollutants may reduce T-suppressor cell activity and this might lead to an increase in B cell activity and allergic phenomena but the Committee on the medical effects of air pollutants (Committee on the medical effects of air pollutants, 1995) concluded that volunteer studies have not shown any synergistic effect with combinations of air pollutants.

In the UK the pollen count in London has fallen, rather than risen over the last 30 years (Emberlin et al., 1993) and is unlikely to be a factor in itself. One hypothesis has been that pollution may alter the antigenicity of pollen (Ruffin et al., 1984). Whether pollution acts as a hapten or as an irritant making tight cell junctions "looser" is not known. Air pollutants include SO_2 that is derived primarily from coal burning and volcanoes and a measurement of intensity of winter smog (Committee on the medical effects of air pollutants, 1995), ozone which is formed by high temperature and sunlight on NO_2 with hydrocarbons, NO_2 which comes from car exhausts and fuel combustion and is an indicator of vehicle smog, acid aerosols such as sulphuric acid, nitric acid and hydrochloric acid, and particles (Wardlaw, 1997) (Schlesinger, 1992). Airborne particles can be primary, being emitted from power stations, cars or factories or they can be secondary, formed by condensation within the atmosphere as a result of a chemical reaction (Committee on the medical effects of air pollutants, 1995). Particulate pollution in the UK is primarily from inefficient combustion of coal and in particular domestic fires. The relationship between pollutants is complex. There is a strong negative correlation between ozone and both NO_2 and the oxides of nitrogen but few other correlations with other pollutants exist (Advisory group on the medical aspects of air pollution episodes: fourth report, 1995). Only particles less than 10μm are able to get to the lungs. Inert particles on their own have been reported as having no effect on nasal airflow after 6 hours (Andersen and Proctor, 1982) although animal studies suggest that IgE production increases in the presence of particulate matter (Murancka et al., 1986; Takafuki et al., 1987; Bascom et al., 1990; Peden et al., 1994). Peden et al. (Peden et al., 1995) found that when individuals with allergic rhinitis were exposed to ozone at 400ppb they had an increase in their eosinophilia on nasal lavage. Work studying diesel exhaust particles has shown that they can induce local mRNA for Interleukin (IL)-2,4,5,6,10,13 and IFN-γ protein production in control patients and patients with allergic rhinitis (Diaz-Sanchez et al., 1994), and can cause raised IgE levels in smokers compared to non-smokers (Jensen et al., 1992). McKeever et al. found that maternal smoking had no effect (McKeever et al., 2002) Rusznak et al. (Rusznak et al., 1994) have suggested that preliminary exposure to NO_2 and Ozone may have a priming effect and increase nasal response to pollen delivered later. Wang et al. (Wang et al., 1995) showed that acute exposure to NO_2 may "prime" eosinophils for subsequent allergen activation in patients with allergic rhinitis. It is possible that interactions between pollutants may have been underestimated due to the low concentrations of pollutants studied and the confounding effects of prior exposure to ambient pollutants (Committee on the medical effects of air pollutants, 1995).

The relationship between asthma and allergic rhinitis

In some studies allergic rhinitis has been shown to preceed the development of asthma (Anderson et al., 1986; Wright et al., 1994;). Allergic rhinitis and allergic asthma usually have the markers of atopy and whilst they often occur together it is unclear why some patients exhibit allergic rhinitis whilst others have asthma or both (Braunstahl et al., 2003). The relationship between allergic rhinitis and asthma is strong and there is good evidence that the resolution of asthma correlated well with an improvement in hay fever (Greisner et al., 2000).

Summary

There is good evidence that our genome has a pervasive influence upon our likelihood of developing the markers of atopy. It appears that several genes are involved, each contributing to the risk of the carrier developing rhinitis (Cookson et al., 1989; Daniels et al., 1996). However, genes do not work in isolation. They work in the context of the variations in all the other genes carried by that individual and the environment to which the individual is exposed.

The epidemiology that has examined the increase in allergic rhinitis, along with the variables that may be responsible for these changes or be markers of hitherto unknown aetiological factors, appears to be a hopeful direction for research. In conjunction with this the molecular biology of allergic rhinitis is helping us to understand what is happening at the cellular level although it seems likely that the Th1/Th2 paradigm is too simplistic to explain the spectrum of disease. Why do some individuals with the markers of atopy have symptoms whilst others do not? Why and how do individuals develop allergic symptoms and the majority resolve with ageing? We have much to find out.

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