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Papers

Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis a virus

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Abstract

Objective: To investigate the working hypothesis that common infections occurring early in life prevent atopy.

Design: Cross sectional, retrospective study of young Italian men with results for hepatitis A serology and atopy.

Setting: Air force school for military students in Caserta, Italy.

Subjects: 1659 male students aged 17-24, most of whom (90%) were from central and southern Italy.

Main outcome measures: Skin sensitisation and specific IgE antibodies to locally relevant airborne allergens; diagnosis of respiratory allergy (asthma or rhinitis, or both); hepatitis A seropositivity.

Results: 443 of the 1659 subjects (26.7%) were positive for hepatitis A virus antibody. Atopy was less common among seropositive than

seronegative subjects according to skin sensitization (weal reaction ≥ 3 mm) to one or more allergens (21.9% (97/443) v 30.2% (367/1216), $P < 0.001$); polysensitisation (sensitive to three or more allergens) (2.7% (12/443) v 6.4% (78/1216), $P < 0.01$); high specific IgE concentration (9.7% (43/443) v 18.4% (224/1216), $P < 0.00005$); and lifetime prevalence of allergic rhinitis or asthma, or both (8.4% (37/443) v 16.7% (203/1216), $P < 0.001$). Hepatitis A seropositivity remained inversely associated with atopy after adjusting for father's education, the number of older siblings, and the area of residence (based on the number of inhabitants). The prevalence of atopy was constantly low among seropositive subjects, whatever the number of older siblings; by contrast, it increased with a decreasing number of older siblings among seronegative subjects.

Conclusion: Indirect but important evidence is added to the working hypothesis as common infections acquired early in life because of the presence of many older siblings (among seronegative subjects) or because of unhygienic living conditions (among seropositive subjects) may have reduced the risk of developing atopy.

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Key messages

- Young men with antibodies to hepatitis A virus had a lower prevalence of atopy and atopic respiratory diseases, and this was independent of the number of older siblings and other relevant risk factors
- The prevalence of atopy was as low in seronegative as in seropositive subjects only when they had three or more older siblings
- Among seropositive subjects the prevalence of atopy was low, whatever the number of older siblings
- Common infections acquired early in life because of the presence of many older siblings (among seronegative subjects) or because of unhygienic living conditions (among seropositive subjects) may have reduced the risk of development of atopy
- This study adds indirect but important evidence to the hypothesis that improvements in hygiene and reduced recirculation of common infections may be a major cause of the increasing prevalence of atopy and atopic diseases in Western countries

Introduction

In the Western world the prevalences of allergic rhinitis and asthma have increased significantly in the past decades, especially among younger people.¹ Reasons for such a trend are still poorly understood, but they may be related to a parallel increase in IgE sensitisation towards common airborne allergens.²

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In a British cohort study Strachan and colleagues observed an inverse relation between the number of older siblings and atopy or atopic diseases and hypothesised that protection from atopy might be exerted by infections acquired early and often during childhood as the result of unhygienic contact with older siblings.^{3 4 5 6} This hypothesis would be consistent with current expanding knowledge on the regulation of the IgE immune response in humans,⁷ which suggests that stimulation of TH1-like lymphocytes by infection could physiologically inhibit the clonal expansion of allergen specific TH2-like lymphocytes at a critical time during infancy.^{6 8} On the basis of these and other recent studies, declining exposure to infections early in life has been proposed as the most relevant characteristic of Western lifestyle in determining the increasing prevalence of allergy.^{6 9 10}

High recirculation of infectious agents is associated with environmental conditions such as overcrowding, poor hygiene in handling food, and infrequent washing. One of the most reliable markers of being brought up unhygienically or having been exposed to an infectious environment is considered in southern Europe to be the presence of antibodies to hepatitis A virus.¹¹

We tested the above working hypothesis by analysing the relation between the presence of hepatitis A antibodies and atopy in a population of 1659 Italian military students whose family structure, residence, father's education, atopy, and hepatitis A serology were already available.^{12 13}

Subjects and methods

Population sample

During October 1990 to June 1991 we examined 1887 Italian military students attending the Italian air force's school for non-commissioned officers in Caserta, Italy. Allergy and lung function were not assessed before entry, so candidates with allergy had not been excluded. Over 90% of subjects came from central and southern Italy. After giving their

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informed consent 1815 (96.2%) subjects participated in an epidemiological study on respiratory allergic diseases, whose details have been published elsewhere.¹² Of these, 1268 had also participated in a survey on the incidence of hepatitis A.¹³

This study is a retrospective analysis of data, most of which were acquired in these previous surveys and were further completed by collecting missing information on the family structure of all participants and by testing for antibodies to hepatitis A virus in 391 subjects who had participated only in the allergy study but whose serum samples were still available. We used the same commercial assay on aliquots of serum, which were obtained in October 1990 and had been stored since then at -70°C. The final number of subjects examined in this study was 1659 (mean age 20.7 (SD 1.6)), corresponding to 87.9% of those attending the course. There were no differences in known characteristics between those who did and those who did not complete this study.

Demographic data

Demographic data and information on the family structure, father's education, and area of residence (determined as the number of inhabitants in the area) were ascertained from a standard questionnaire.

Skin tests

A panel of seven airborne allergens (mixed grass pollens, *Parietaria judaica*, *Artemisia vulgaris*, *Olea europaea*, *Alternaria alternata*, *Dermatophagoides pteronyssinus*, and cat epithelium (Standard Quality line, Pharmacia, Uppsala, Sweden) were used for immediate skin prick tests in all the participants, as previously reported.¹³ For the purposes of the present study a weal reaction greater than or equal to 3 mm after subtraction of the negative control reaction was regarded as positive.

Serological assays

Blood specimens were taken from all participants, and serum samples were stored at -70°C. A fluorescence, solid phase multiallergen immunoassay (Phadiatop-CAP, Pharmacia, Uppsala) was used to evaluate the overall degree of IgE sensitisation to inhalant allergens as previously validated in this population sample.¹³ The results were expressed as the logarithm of ratio units obtained from the formula: $\log(\text{fluorescence units of sample} / \text{fluorescence units of reference serum})$.

The semiquantitative interpretation of multiallergen immunoassays has been recently introduced both in epidemiological and in genetic studies on allergy.^{13 14}

All serum samples were tested for total antibodies to hepatitis A virus by a commercial immunoenzyme assay (HABA, Abbott, IL). Positivity or negativity was assigned according to the kit's instructions.

Diagnosis of allergic rhinitis and asthma

A clinical diagnosis of allergic rhinitis and asthma was based on history (a standardised questionnaire administered by one of us (PMM)), physical examination, and skin test results, as reported

elsewhere.¹³ Allergic rhinitis or conjunctivitis was diagnosed in subjects with a history of rhinitis apart from colds, such rhinitis being characterised by rhinorrhoea and sneezing with or without watery, itchy eyes that lasted for three weeks or more during the allergy season or occurred non-seasonally but in association with exposure to specific triggers and that was related to sensitisation to airborne allergens. Allergic asthma was diagnosed in subjects who had a history of repeated episodes of coughing, dyspnoea, wheezing, and chest tightness (or whistling) that were not caused by any organic condition, that occurred during the pollen season or recurrently if the subject was continuously exposed to specific triggers, and that were related to the sensitisation to airborne allergens. We considered asthma or rhinitis to be present if disease was current or if there was a documented history of having had it, or both.

Statistical methods

The association between each study factor and skin sensitisation, serum IgE sensitisation, and respiratory allergic disease was evaluated by estimating the prevalence odds ratio. Confidence limits, χ^2 tests, and test for trends were calculated by EpiInfo. To estimate the independent effect of each study factor on atopy the adjusted odds ratio was calculated by logistic regression analysis using the logistic regression program of biomedical data processing.¹⁵



Results

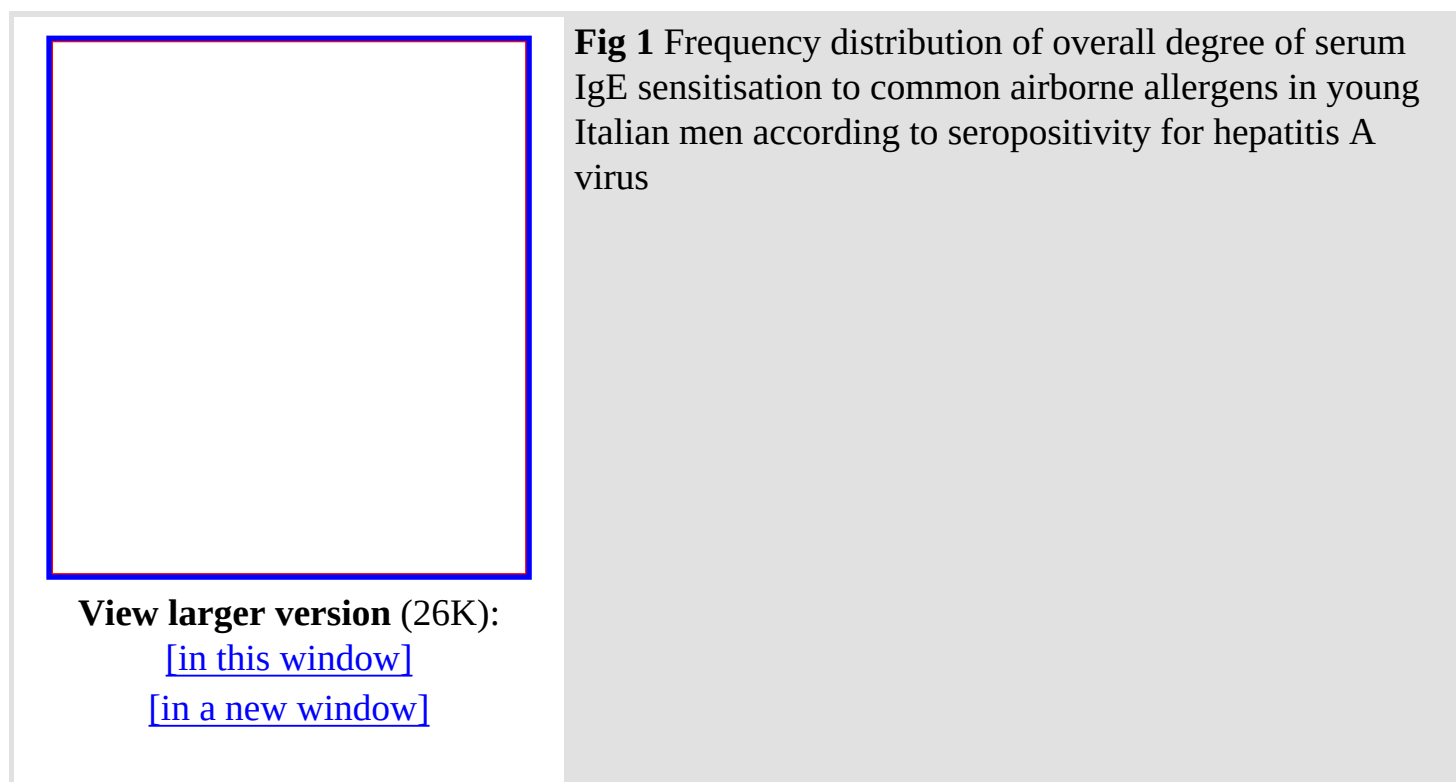
In all, 443 of the 1659 subjects (26.7%) had antibodies to hepatitis A virus. Only 97 of the 443 subjects with antibodies (21.9%) had a positive weal reaction to at least one of the seven aeroallergens tested, compared with 367 of the 1216 subjects without antibodies (30.2%) (P<0.001). For each of the allergens tested a positive reaction was likely in subjects without antibodies to hepatitis A virus, with a significant difference for *Dermatophagoides pteronyssinus*, grass pollens, and cat epithelium.

Interestingly, differences between the two groups increased with the number of positive reactions. When the total weal reaction was taken into consideration, the difference in the prevalence of positive reactions between the two groups increased with increasing total weal size (table 1).

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View this table: [in this window] [in a new window]	Table 1 Skin sensitisation to common airborne allergens, specific IgE concentrations, and respiratory allergy in 1659 Italian military students according to presence of antibodies to hepatitis A virus. Values are numbers (percentages) of subjects
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Figure 1 shows the frequency distribution curves of the overall serum concentration of IgE against common airborne allergens. Interestingly, the frequency distribution curve of the seronegative group but not that of the seropositive group peaked at the higher concentrations of specific IgE. This peak occurred at a log ratio unit of 1.5 (range 1.2-1.8); for simplicity we therefore took a log ratio unit of IgE greater than 1.2 (which corresponded to about log 8 fluorescence units and 10 ku/l of overall specific IgE (data not shown)) to mean a high overall degree of sensitisation to airborne allergens (high specific IgE concentration); this cut off point identified as positive most subjects with polysensitisation and with clinical atopy.¹³



The prevalence of allergic rhinitis or asthma, or both, was significantly higher in the seronegative than in the seropositive group (16.7% v 8.35%; odds ratio 2.20 (95% confidence interval 1.50 to 3.24)) (table 1).

A multivariate analysis including several relevant sociodemographic variables, such as father's education, number of siblings, number of inhabitants in the area of residence, and age, is shown in table 2). Subjects who were seronegative for hepatitis A virus were more likely to be affected by atopic sensitisation than those who were seropositive (odds ratio 1.98 (1.37 to 2.86)), after adjustment for the confounding effect of sociodemographic characteristics such as the number of older or younger siblings, age, paternal education, and area of residence (table 2). The number of older siblings was another relevant independent factor inversely associated with the prevalence of atopy, but the number of younger siblings was not significantly associated (table 2).

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Table 2 High specific IgE concentration to common airborne allergens in 1659 Italian military students according to presence of antibodies to hepatitis A virus and to relevant sociodemographic factors

The prevalence of atopy was inversely related to the number of siblings among seronegative but not seropositive subjects (χ^2 test for trend; $P < 0.01$) (fig 2). In the seropositive group the prevalence of atopy was around 9% and was independent of the number of older siblings.



Fig 2 Prevalence of atopy (log ratio unit >1.2) in relation to number of older siblings in seropositive and seronegative subjects

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Discussion

Inverse association between seropositivity for hepatitis A antibodies and atopy

We found an inverse association between antibodies to hepatitis A virus and atopy in a population of 1659 Italian military students, and this persisted after adjustment for relevant sociodemographic factors, including family size and number of older siblings, age, area of residence (number of inhabitants), and father's education. Lower prevalence of atopy among seropositive subjects had four characteristics.

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1. It was confirmed both from skin sensitisation tests and by serum specific IgE assay.
2. It was not limited to a single allergen, suggesting a modification in host susceptibility to sensitisation rather than a lower exposure to some specific allergens.
3. (3) It was more pronounced with higher concentrations of specific IgE or skin test weal sum, thus implying a high specificity.
4. (4) It was paralleled by a consistently reduced prevalence of allergic rhinitis and asthma, thus implying clinical relevance.
5. To our knowledge, this is the first observation within one population of a Western country, of an inverse association between serological evidence of a given infection and allergy.

Association and working hypothesis

In the same population we also observed a strong inverse association between the number of older siblings and atopy, and this persisted after adjustment for hepatitis A serology. According to the working hypothesis, these data suggest that hepatitis A is not the only infection associated with low prevalence of atopy. Interestingly, after stratification for hepatitis A serology the protective effect of older siblings disappeared among seropositive subjects.

Taken together, these data suggest two things. Firstly, in people whose living conditions were hygienic enough to prevent infection with hepatitis A virus the presence of older siblings was necessary to reap the benefit of infections at an age early enough to confer protection from atopy. Secondly, in subjects infected by hepatitis A virus, this and other common infections may have been transmitted so frequently and early as to induce protection from atopy, independently from the number of older siblings. Hepatitis A was endemic in Italy during the 1970s, and it was usually acquired early in childhood, most commonly without inducing symptoms¹⁶; moreover, its transmission was favoured by faecal contamination of the living environment, poor hygienic food handling, day care settings, etc, which all facilitate the transmission of many other infectious agents. Thus, a possible conclusion is that the correlations observed strongly support the working hypothesis even if the temporal relations of hepatitis A with events leading to atopy are not directly shown in our study. Nevertheless, other possible explanations must be considered.

Other explanations

Hepatitis A seropositivity could simply be an indicator of lower exposure to risk factors for atopy (pollution, high indoor allergen concentration, smoke).¹⁷ However, the potential confounding effect of outdoor pollution was indirectly adjusted for by including the number of inhabitants of the place of residence in the logistic analysis; a higher exposure to indoor allergens would have not affected sensitisation to pollen; and active smoking was not associated with atopy (data not shown), though we have no data on passive smoking.

Other studies

Published work shows a consistent inverse relation between current hepatitis A seropositivity and the prevalence of respiratory allergy in different parts of the world, as well as opposite trends over the past decades in Western countries. More interestingly, during the 1970s in the United States the prevalence of hepatitis A seropositivity was high in older people but low in younger people,¹⁸ whereas the opposite was true for atopy.¹⁹ This example suggests how the prevalence of atopy in a given generation of subjects may reflect their overall exposure to common infectious agents (such as hepatitis A virus) during their infancy, as previously postulated.⁶ Therefore, as an indicator of exposure to common infections, hepatitis A seropositivity may be useful in testing the working hypothesis in other countries.

Infection(s) that may prevent atopy

Our data do not allow conclusions on the type of infection(s) that reduce the risk of atopy.

Interestingly, studies in Guinea-Bissau suggest that measles may prevent atopy.²⁰ This would imply that a single measles episode is sufficient to influence the immune response to airborne allergens for many years ahead. Although obtained in a completely different population, our data do not refute this conclusion. Indeed, measles might have occurred much earlier than in the remaining population sample in those subjects whose living conditions had also favoured transmission of hepatitis A virus, as well as in subjects who were never infected with hepatitis A virus but had many older siblings.

Nevertheless, our data question whether a more complex and protracted sequence of infectious events, consisting of repeated contacts with various pathogens, is necessary to significantly affect the TH1-TH2 equilibrium in the immune response to airborne allergens. The inverse relation between hepatitis A infection and atopy reported here suggests that infections transmitted through the faecal-oral route might also help to prevent atopy and atopic diseases. Without any more direct evidence, however, the kinds of infections and their possible interaction with processes leading to atopy remain to be clarified.



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