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ORIGINAL ARTICLE

German cattle allergy study (CAS): public health relevance of cattle-allergic farmers

Astrid R. R. Heutelbeck · Nico Janicke · Reinhard Hilgers · Birgitta Kütting · Hans Drexler · Ernst Hallier · Heike Bickeböller

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Abstract
Introduction Allergic reactions caused by animals are a common and significant occupational health concern. In a large population-based study on occupational asthma in Europe, farming has been among the occupations with the highest risk.
Objectives Characteristics of cattle-allergic farmers are described in a retrospective observational design.
Methods The study covers farmers from all regions of Germany which were reported to the Agricultural Institutions for Statutory Accident Insurance and Prevention (Landwirtschaftliche Berufsgenossenschaften, LBGs) between 1990 (January) and 2002 (December) with a suspected occupational cattle-allergic airways disease. For these farmers, the following parameters were considered: age, gender, onset of airways symptoms related to contact with cattle, begin of employment disability, total and specific Immunoglobulin E (IgE) against cattle allergens, and results of lung function measurements.
Results A total of 513 patients (age 14–74, mean 40.7 years; 45.6% women, 54.4% men) had been reported for a suspected occupational cattle-allergic airways disease. Of these patients 24.8% showed cattle-related symptoms of asthma, 11.7% of rhinitis, and 60% of both asthma and rhinitis, while only 34.5% of all reported patients showed an airways obstruction in the first documented lung function test. A total of 62.5% out of the group of patients with an officially recognized occupational disease (42.1%, $n = 216$) have an initial employment disability with a rating of 20% or above.
Conclusions Our results underline the high public health relevance of cattle allergy in farmers, especially in the light of the large number of young patients. Considering the known difficulties in diagnosing cattle allergy due to the number of false negative test results, we are convinced that its relevance is even higher than the number of reported cases suggests. The high rate of initial employment disability among the affected patients underlines the need for improved preventive measures.

Keywords Cattle allergy · Occupational disease · Employment disability · Prevention

A. R. R. Heutelbeck (✉) · E. Hallier
Abteilung Arbeits- und Sozialmedizin,
Georg-August-Universität, Waldweg 37,
37073 Göttingen, Germany
e-mail: aheutel@gwdg.de

N. Janicke
Institut für Mathematische Stochastik,
Abteilung Genetische Epidemiologie,
Georg-August-Universität, Humboldtallee 32,
37073 Göttingen, Germany

H. Bickeböller
Abteilung Genetische Epidemiologie,
Georg-August-Universität, Humboldtallee 32,
37073 Göttingen, Germany

R. Hilgers
Abteilung Medizinische Statistik, Georg-August-Universität,
Humboldtallee 32, 37073 Göttingen, Germany

B. Kütting · H. Drexler
Institut für Arbeits-, Sozial- und Umweltmedizin,
Friedrich Alexander Universität Erlangen-Nürnberg,
Schillerstr. 25+29, 91054 Erlangen, Germany

Introduction

Allergic occupational airways diseases are annually among the five most frequently reported occupational diseases in all industrial sectors according to the accident prevention record of the German Federal Ministry of Labour and

Social Affairs (*Bundesministerium für Arbeit und Soziales*). The symptoms vary among workers from mild rhinitis to serious attacks of asthma. In the last years, the cases in the agricultural sector accounted for about 5% of the reported occupational diseases in all industrial sectors.

In a large population-based study on occupational asthma in Europe, farming has been among the occupations with the highest risk (Kogevinas et al. 1999). In their workplaces, farmers are exposed to a large amount of allergens and immunotoxicants which can induce the development of occupational allergic airways diseases (Gassner 1996; Rylander and Peterson 1994). The high prevalence in the general population of type I allergy to common agents such as dog or cat allergens shows that especially animal proteins have a strong allergic effect. Allergic reactions to animals are also a common and significant occupational health concern (Seward 1999).

Dairy farming forms the centre of agriculture in many regions and thus also the focus of occupational health concerns. While several case reports have covered specific allergies, the prevalence of sensitization and/or symptomatic allergy to cows in agricultural populations, however, has been assessed in only a small number of studies. In Finland, where all new cases of occupational disease are reported to the National Register; animal epithelia (especially cow dander), cereal flour, and grain have been leading causes of occupational asthma and rhinitis, accounting for about a half to two-third of new cases (Reijula and Patterson 1994; Karjalainen et al. 2000). Other investigations on farmers in northern Europe found 5–14% of asymptomatic farmers sensitized to cow allergens (Terho et al. 1985; Rautalahti et al. 1987; van Hage-Hamsten et al. 1987; Iversen and Pedersen 1990).

Cattle-allergic patients with rhinitis and asthma are of major importance to the Agricultural Institutions for Statutory Accident Insurance and Prevention (*Landwirtschaftliche Berufsgenossenschaften*, the "LBGs") in Germany, as they impel more frequent and more extensive prevention measures compared to other occupational diseases. Every fifth patient reported to the LBGs showed work-related asthmatic symptoms. The diagnosis of occupational asthma often goes along with negative economic consequences: ending the exposure to the agents that cause the symptoms can also mean losing work-related income, depending on unemployment benefits despite coverage by a workers' compensation system, and possibly undergoing occupational retraining. Continuing to work in the same job, on the other hand, usually results in an increased severity of the asthmatic symptoms. In both cases, the costs for occupational asthma (including occupational disability pensions as well as medical and technical expenses) are high, and they are expected to rise with the increasing prevalence of the disease (Moscato and Rampulla 2003).

Despite the high public health relevance of obstructive airways diseases, effective prevention strategies for occupational asthma are rare. In order to provide improved preventive measures, the decisive genetic and non-genetic factors (such as environmental influences at the workplaces) have to be identified. Identifying and modifying these decisive factors will help to implement measures of secondary and tertiary prevention for symptomatic individuals as well as primary preventive measures for exposed non-symptomatic workers.

Objectives

This study describes the characteristics of the population, such as the distribution of age, gender, atopic predisposition, and degree of asthma reflected by lung function and the employment disability. Based on this information, the study analyses the different surroundings and individual parameters of persons that were reported with a suspected cattle-allergic airways disease in Germany.

Methods

Report and recognition of occupational airways diseases in Germany

The German law forms the legal framework for reporting and recognizing occupational diseases (Baur et al. 1998): physicians, employers, or employees themselves can submit a report indicating the suspicion of an occupational disease to the LBGs. Based on the opinions of medical specialists, the LBG decides whether or not to officially recognize the reported disease as an occupational disease. In Germany, allergic airways diseases are included in the official list of (in total 68) occupational diseases. An allergic airways disease, can however, only be officially recognized as occupational disease after the patient has given up "all occupational activities that led to the development, aggravation or recurrence of the disease". An exception to this rule is only made in cases of severe hardship where the patient is forced to use a breathing mask or similar technical equipment for all tasks. Once the occupational disease has been officially recognized, the employment disability rating is estimated based on the individual severity of the disease. Patients having an employment disability with a rating of 20% or above will subsequently receive a monthly pension.

Subjects of the study

The study includes patients from all regions of Germany who work in agriculture and who meet the following criteria:

- The case of the patient has been reported to the LBGs between 1990 (January) and 2002 (December).
- The reason for the report was either a diagnosed occupational rhinitis or obstructive airways disease.
- The patient was reported with a suspected occupational cattle allergy.

Data basis of the study

Currently, Germany has a network of ten regional LBGs: Lower Saxony–Bremen, North Rhine Westphalia, Hesse–Rhineland Palatinate–Saarland, Franconia–Upper Bavaria, Lower Bavaria–Upper Palatinate, Swabia, Baden–Wuerttemberg, Berlin, Saxony and Schleswig-Holstein (the "regions"). Each reported case is kept in a single file with the competent regional LBG. In a retrospective, observational, descriptive design, all information on the relevant reported cases was collected.

This epidemiological study follows the basic principles of retrolective cohort studies that are internationally established within the framework of epidemiological methods. Cohort studies involve a defined population of patients followed forward in time. They evaluate the potential predictors, demography, risk, exposure, treatment, and confounding variables for each patient at the beginning as well as the subsequent development of the disease in the course of the study (Feinstein 1985; Grimes and Schulz 2002). Retrolective cohort studies usually have the advantage of being substantially larger, much less expensive and less time-consuming than prospective studies. To our knowledge, this study is the first study of this kind on this subject.

The files of the relevant reported farmers were evaluated with respect to the following aspects: individual medical history, allergological and pneumological diagnostic results, work history, and technical conditions of the individual farming environment. Besides, aspects of the occupational disease liability compensation case were considered. Based on the files, the data was combined anonymously in a database, including age, gender, and region of residence. Cattle-related symptoms of the upper airways (such as itchy and stuffy nose or sneezing) and the lower airways (shortness of breath, asthma, cough) were recorded, and information on the development of the disease and its recognition as occupational disease (including the employment disability rating) was also included.

When processing data from the LBGs, we faced several difficulties, most importantly a lack of standardization in the process of collecting, reporting, and administering the data. The files differ from region to region, also due to different diagnostic methods and different forms of medical or technical reports. The completeness of data for the surveyed time period constituted another major problem in the East of Germany where the LBGs had been established only in the early 1990s.

All data for this study has been collected with the approval of the Ethic Committee of the Georg-August-University of Göttingen, Germany.

Diagnostic parameters

Age, gender, and onset of airways symptoms (such as rhinitis and asthma) related to contact with cattle were considered for all patients.

Based on the diagnostic data in each report, all skin tests with cattle allergens (including tests with different commercial as well as self-prepared extracts) were categorized as positive or negative with regard to cattle allergens. The total IgE values (based on commercially available enzyme or radioimmuno assays) were documented in international units/ml or kU/l. Based on the total IgE values, the population was subdivided into three categories of patients showing values lower than and equal/above 100 kU/l in the initial test according to the published recommendations (Zetterström and Johansson 1981): non-atopic persons with initial IgE values below/equal 20 kU/l, patients with initial IgE values above 20 kU/l and below 100 kU/l, and atopic patients with initial IgE values equal/above 100 kU/l.

Using the same base of diagnostic data from the reports, all lung function tests (spirometry and/or body plethysmography tests) were evaluated in line with the published reference values (Quanjer et al. 1993). Based on the maximum achieved forced expiratory volume in one second (FEV1) in percent of the predicted values, the population was subdivided into four categories according to the severity of asthma documented in the initial test following the published recommendations (Kroidl et al. 2000): First, patients with non-obstructive lung function (initial FEV1 values above 80%) and patients with obstructive lung function (initial FEV1 values below/equal 80%) were differentiated. Second, patients with obstructive lung function were further differentiated according to the degree of obstruction: patients with slight obstruction (FEV1 values below/equal 80% and above 70%), patients with medium obstruction (FEV1 values below/equal 70% and above 50%), and patients with severe obstruction (FEV1 values below/equal 50%).

Finally, all patients with a recognized occupational airways disease were categorized according to their initial employment disability rating. The population was subdivided into three categories: patients with an initial employment disability rating below 20% and patients with an initial employment disability rating equal/above 20%.

Statistical methods

We analyzed all collected data with the statistic program R (R Development Core Team 2003) and SPSS. For descriptive statistics, mean, median, interquartile range, and range are given. The interquartile range is defined as the difference between the 25 and 75% quartiles. The range refers to the difference between minimum and maximum values in the collected data. The age distribution is determined by the difference between the year of birth and the year in which the relevant parameters (such as total IgE and lung function values) initially occurred. The sample sizes are explicitly given with each calculation, as they differ in some instances for the reason of incomplete data in the files. Whenever appropriate, the results are given for Germany as a whole as well as for each of the ten regions.

Results

Study population

A total of 513 patients had been reported to the LBGs in Germany between 1990 (January) and 2002 (December) with a suspected occupational cattle-allergic airways disease (study population). While almost all of them were farmers, a few veterinarians or workers involved in artificial insemination are also included in this group. For the purpose of this study, all of them will be referred to as patients or farmers.

The patients were, at the time of the report, between 14 and 74 years old (range; mean 40.7 years, median 39.0 years, interquartile range 31.0–51.0 years). Of these patients 45.6% ($n = 234$) were women, 54.4% ($n = 279$) were men. According to the reports, 24.8% ($n = 127$) of the patients showed cattle-related symptoms of asthma, 11.7% ($n = 60$) of rhinitis, and 60.0% ($n = 308$) of both asthma and rhinitis. For 3.5% ($n = 18$) of the patients, no cattle-related symptoms, but a clear diagnosis of cattle allergy based on the results of allergic diagnostics were documented.

The cases of cattle-allergic patients account for 9.1% of all 5,627 cases that were reported to the LBGs in the timeframe covered by this study with a suspected allergic airways disease. This proportion varies in the different regions between 4.1 and 18.7% (Table 1). The north-western and south-eastern regions of Germany show the highest numbers of documented cases (Table 1).

Skin test results

Results of skin tests with cattle allergens (including 460 tests with different commercial and 118 tests with self-prepared extracts) were documented in the files of 511 patients, showing a sensitization to cow allergens in 95% ($n = 483$) of these cases; 5% ($n = 28$) of the cases were reported without cattle allergen skin tests. Positive skin test results were documented in 460 cases with commercial extracts. For 9 of the 34 farmers with negative skin test results, additional skin tests with self-prepared extracts were performed, showing adverse positive results in 8 cases (89%; Table 2). Differences can be found between the test results achieved with commercial and self-prepared extracts were shown in Table 2.

Table 1 Regional distribution of cases of occupational airways diseases and occupational cattle-allergic airways diseases

	Cases of occupational allergic airways diseases			
	All	Cattle-allergic		
	A: Reported	B: Reported	C: Recognized	D: Recognized (Employment disability rating >20 %)
Regions	*n*	*n* (% of A)	*n* (% of B)	*n* (% of C)
Germany	5,627	513 (9.1 %)	216 (42.0 %)	135 (62.5 %)
Lower Saxony–Bremen	1,188	92 (7.7 %)	31(33.7 %)	14 (45.2 %)
North Rhine Westphalia	929	41(4.4 %)	9(22.0 %)	6(66.7 %)
Hesse	583	24 (4.1 %)	23 (95.8 %)	20 (87.0 %)
Franconia–Upper Bavaria	646	101 (15.6 %)	37 (36.6 %)	23 (62.2 %)
Lower Bavaria–Upper Palatinate	337	63 (18.7 %)	31 (49.2 %)	17 (54.8 %)
Swabia	489	45 (9.2 %)	32 (71.1 %)	26 (81.3 %)
Baden–Wuerttemberg	541	56 (10.4 %)	13 (23.2 %)	9 (69.2 %)
Berlin	458	45 (9.8 %)	20 (44.4 %)	8 (40.0 %)
Saxony	120	15 (12.5 %)	7 (46.7 %)	5 (71.4 %)
Schleswig–Holstein	336	31 (9.2 %)	13 (41.9 %)	7 (53.8 %)

Table 2 Comparison of test results achieved with commercial and self-prepared extracts

Test results with commercial Extracts	Test results with self-prepared extracts	
Positive (n = 143)	Positive (n)	126 (88.1%)
	Negative (n)	17 (11.9%)
Negative (n = 9)	Positive (n)	8 (88.9 %)
	Negative (n)	1 (11.1 %)
Not tested (n = 5)	Positive (n)	3 (60 %)
	Negative (n)	2 (40 %)

Total IgE determinations were documented in the files of 414 patients (80.7%), lying between 3 and 10,697 kU/l (range; mean 418.1 kU/l, median 213.5 kU/l, interquartile range 90.0–508.8 kU/l). The age distribution in the group of patients with document IgE determinations was comparable to that of the study population (mean 40.5 years, median 38.5 years, interquartile range 31.0–51.0 years, range 14.0–75.0 years). Of the patients in this group 3.9% (n = 16) showed an initial total IgE value below/equal 20 kU/l, 24.4% (n = 101) above 20 kU/l and below/equal 99 kU/l, and 71.7% (n = 297) above 100 kU/l.

Lung function measurements

Lung function measurements were documented in the files of 495 patients (96.5%). Again, the age distribution in the group of patients with documented lung function measurements was comparable to that of the study population (mean 40.5 years, median 39.0 years, interquartile range 31.0–50.5 years, range 14.0–74.0 years). For 34.5% (n = 171) of the patients in this group, an obstructive lung function was documented in the first lung function measurement in the file: 11.1% (n = 55) showed a slight obstruction, 12.7% (n = 63) a medium obstruction, and 7.7% (n = 38) a severe obstruction [the degree of obstruction was not documented in 15 cases (3.0%)]. Comparing the age distribution in the groups of patients with non-obstructive lung function (mean 38.1 years, median 36 years, interquartile range 30.0–44.0 years, range 14.0–68.0 years) and obstructive lung function (mean 45.1 years, median 48.0 years, interquartile range 35.5–55.5 years, range 15.0–74.0 years), a significant shift upwards of the age of patients in the latter group must be noted (difference in the interquartile range of 11 years) (Fig. 1).

Recognition of occupational airways diseases

An occupational airways disease has been officially recognized for 216 patients (42.1%, cf. above, Table 1). The age of these patients at the time of recognition is slightly higher compared to the age of all patients in the study population, with the interquartile range in the age distribution shifting upwards 4–5 years (mean 44.7 years, median 44.0 years, interquartile range 35.0–56.0 years, range 19.0–73.0 years).

The initial employment disability rating was documented in the files of 207 patients, ranging from 0 to 70 % (range, mean 18.6%, median 20%, interquartile range 0–30%). The age distribution in the group of patients with documented employment disability rating was comparable to that of the group of patients with a recognized occupational airways disesase (mean 44.5 years, median 44.5 years, interquartile range 34.3–55.0 years, range 19.0–74.0 years). The reasons for the missing information on the disability rating in nine files vary (e.g. a recognition of an occupational airways disease based on other, incomplete data).

For 62.5 % (n = 135) of the patients with a recognized occupational airways disease, the initial employment disability rating was 20% or above (median 20%, interquartile range 20–30%, range 20–70%). The proportion of patients with an employment disability rating of 20% or above varied between the different regions and ranged between 40.0 and 87.0% (cf. above, Table 1). Comparing the age distribution in the groups of patients with an employment dis-

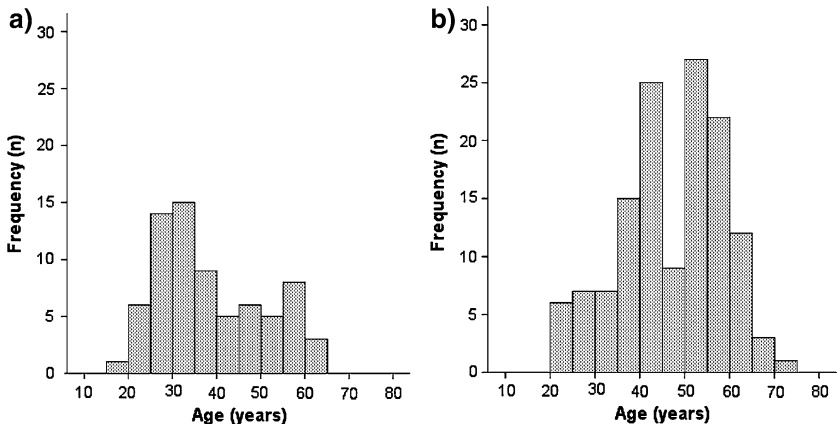

Fig. 1 Age distribution of cattle allergic patients with recognized occupational airways diseases and their employment disability ratings, **a** lower than 20% (n = 72), **b** greater or equal than 20% (n = 135)

ability rating below 20% (mean 39.2 years, median 35.5 years, interquartile range 30–48.8 years, range 19.0–65.0 years) and equal/above 20% (mean 47.5 years, median 49.0 years, interquartile range 40.0–56.8 years, range 22.0–74.0 years), a difference in the interquartile range of 10 years can be found (Fig. 2).

A comparison of the gender distribution between the group of patients with an employment disability rating equal/above 20% (62 women, 73 men), the group of patients with a recognized occupational airways disease (103 women, 113 men) and the study population (234 women, 279 men) revealed no noteworthy differences.

Discussion

The German Cattle Allergy Study (CAS) considers the data of all cases of cattle-allergic patients reported in Germany over a period of more than 10 years. It allows an analysis of general and work-related aspects in the development of cattle allergy as a basis for effectively developing and optimizing preventive measure against occupational cattle-allergic airways disease.

The proportion of cattle-allergic farmers among all farmers reported to the LGBs under suspicion of an allergic airways disease was particularly high in the north-western and south-eastern regions of Germany. In Franconia–Upper Bavaria and Lower Bavaria–Upper Palatinate, the cases of cattle-allergic patients accounted for up to 18.7% of all cases that were reported in the timeframe covered by this study, double the German average. In contrast, this proportion was clearly smaller in North Rhine Westphalia and Hesse, i.e. about half the German average. These striking regional differences are still inexplicable and it can only be speculated that regionally specific working techniques might be of relevance.

The findings of the European Community Respiratory Health Surveys (ERHCS) indicate that the development of asthma is work-related in 10% of all cases (Blanc et al. 1999; Kogevinas et al. 1999), with farming being one of the most relevant risk factors for occupational bronchial hyper responsiveness (Kogevinas et al. 1999).

Results of epidemiological studies focused on dairy farming are rare and hardly comparable due to differences in the data collection procedures. According to the Finnish Register for Occupational Diseases, the incidence rate of asthma caused by animals was one of the highest (174/million p.a.; Karjalainen et al. 2000). This is further substantiated by a study on 93 randomly selected Finnish farmers, with 14% of them sensitized to cow allergens (Rautalahti et al. 1987). In another Finnish study on 185 dairy farmers, 7.7% of the atopic and 3.2% of the non-atopic farmers were sensitized to cow allergens (Terho et al. 1987). In Sweden, 9.9% of tested 440 Swedish farmers in the general rural population were sensitized to cow allergens (van Hage-Hamsten et al. 1987). Of 60 randomly sampled Danish dairy farmers 5% were sensitized to cow allergens according to skin test results, 2% according to RAST results (Iversen and Pedersen 1990).

Farming may be still underestimated, though, as a risk factor for the development of asthma: the results of the Swedish group of the European Community Respiratory Health Survey (ECRHS) show that 13% of all asthmatic patients aged 20–44 years become unemployed or change their occupation (Blanc et al. 1999) and therefore might not be covered in other statistics relating asthma to farming.

In the age distribution of the study population, we noted a double peak and a high proportion of younger adults (25% of the patients were 31 years or younger at the time the report was submitted). Unlike many other chronic diseases which primarily affect older people, asthma disproportionately affects younger people in their working age. This constitutes a paramount public health concern, as up 40% are consequently rated as partially employment-disabled (Blanc et al. 1993, 1996).

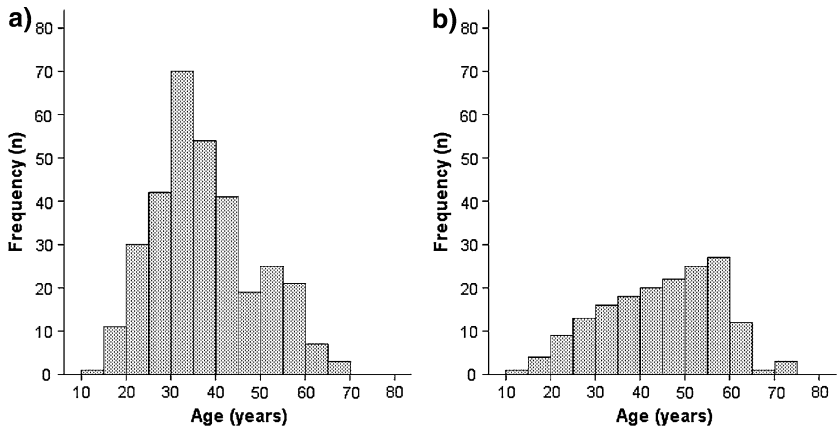

Fig. 2 Age distribution of patients reported with suspected allergic airways disease and lung function values (% of predicted values), **a** FEV1 greater than 80% (n = 324), **b** FEV1 lower or equal than 80% (n = 171)

Even in cases of clearly cattle-related symptoms, results of in vivo and in vitro tests are often inconsistent. In some cases, symptomatic farmers show relevant results with individually-prepared extracts made of hair of their own cattle, but only slight reactions or no reaction at all with commercial extracts. Similar phenomenon have been previously described (Prahl et al. 1978; Ylönen et al. 1990). Such results might be the consequence of a lack of certain important allergens in the applied commercial extract. A total of 34 farmers with clearly cattle-related symptoms showed negative results in allergological testing with commercial extracts. For nine of these farmers, additional tests with individually-prepared extracts were conducted and overwhelmingly showed positive results. In previous investigations, we found positive test results for 32% of the farmers with negative RAST test results, using cow allergens in high concentrations in immunoblotting experiments (Junghans et al. 2003). We have also previously described a relevant protein band of 14 kDa that can be found in allergens of German Simmental, German Brown, and Holstein-Friesian, but that was missing in commercial extracts (Heutelbeck et al. 2001). A lack of relevant proteins in commercial extract may be an explanation for inconsistencies between results of clinical symptoms and in vivo or in vitro diagnostics. If the results of tests with commercial cow allergen extracts are negative, i.e. inconsistent with the observed symptoms, individually-prepared extracts made of hair of the cattle of the patients should be used in for additional testing. In the study population, however, only every fourth patient with cattle-related symptoms and negative test results has been additionally tested with individually-prepared extracts.

We assume that the number of cattle-allergic patients is underestimated as a result of the number of false negative test results observed with commercial extracts, preventing a report of suspicion of an occupational disease to the LBGs. Recommendations on allergological diagnostics should be issued and followed in order to better identify cattle-allergic farmers and to initiate adequate additional measures at the earliest time possible.

Dairy farmers have previously been found to have worse lung function compared to non-farmers (Heller et al. 1986), particularly reflected by a moderate FEV1 decrease over the years (Chaudemanche et al. 2003). Early medical intervention at the onset of an occupational disease should still allow effective measures to prevent manifest obstruction and damage to the lung, The initial FEV1 values that were documented in the files, however, already show an obstructive lung function for every third patient even at the time of first medical intervention. Consequently, the medical surveillance of farmers should be optimized, so that intervention could be made possible in all cases before the lung has been manifestly damaged.

Finally, the high employment disability rating of young patients underlines the need to improve preventive strategies, such as risk screening and early diagnostics. Yet, the suitable preventive measure have to be determined. As long as genetic and immunologic markers as predictors for atopic diseases are not available, it will be difficult to reach a sufficient level of primary prevention. Neither FEV1 measurements nor the determination of bronchial hyper-reactivity were useful in early detection of individuals showing work-related symptoms (Merget et al. 2001). The role of lung function assessments in surveillance programmes is still open for discussion (Malo 2002). Other risk markers for atopy are not yet sufficiently sensitive or specific to justify exclusion of an individual from exposure. As to genetic markers, further information is needed to determine their practical use in medical surveillance programs.

Conclusions

Our results underline the high public health relevance of cattle allergy in farmers, especially in the light of the large number of young patients. Considering the known difficulties in diagnosing cattle allergy related to the number of false negative test results, we presume that its relevance is even higher than the number of reported cases suggests. The high rate of initial employment disability among the affected patients along with the fact that every third patient had an obstructive lung function in the initial test underlines the need for improved preventive measures such as risk screening and early diagnostics. The medical surveillance of farmers should be optimized, so that intervention could still be possible in all cases before the lung has been manifestly damaged.

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