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Are Farming and Animal Exposure Risk Factors for the Development of Granulomatosis With Polyangiitis? Environmental Risk Factors Revisited: A Case-control Study

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ABSTRACT. ***Objective.*** To investigate the possible association between animal exposure and risk for granulomatosis with polyangiitis (GPA).

Methods. Patients with GPA at the Department of Rheumatology, Uppsala University Hospital, between January 1, 2011, and December 31, 2018, were consecutively included. All patients filled in a questionnaire on possible environmental exposures: occupation, hobbies, and animal contact. As controls we included 128 patients with rheumatoid arthritis (RA) and 248 population controls collected from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study, matched for age, sex, and geographical area of residence. The controls filled out a questionnaire on current and past contact with farming and animals, at the time of the RA patient's diagnosis.

Results. A total of 62 patients with GPA, 128 patients with RA, and 248 population controls were included in the study. GPA was significantly associated with horse exposure, with a 2- to 3-fold increased risk compared with RA (OR 3.08, 95% CI 1.34–7.08) and population controls (OR 2.61, 95% CI 1.29–5.29). Borderline increased risks were found for any animal contact, but no association was found when analyzing contact with cats/dogs only. A significant association was found between GPA and farming compared to the population controls (OR 7.60, 95% CI 3.21–17.93).

Conclusion. This study has identified for the first time, to our knowledge, a significant association between exposure to specific animals, namely horses, and the development of GPA. The results also support previous studies reporting an association between farming and GPA, underscoring the possibility of exogenous factors as initiators in the development of GPA.

Key Indexing Terms: environmental risk factors, farming, GPA, horses

Granulomatosis with polyangiitis (GPA) is a systemic necrotizing vasculitis predominantly affecting the airways, lungs, and kidneys but potentially affecting small vessels of any organ.[1] The causes of the disease are poorly understood. A previous genome-wide association study confirmed a genetic contribution.[2] It has also been suggested that various environmental factors are involved in its pathogenesis. Previous studies have demonstrated an association between GPA and exposure to silica and other inhaled agents.[3,4] Additionally, farming has been reported as a risk factor for autoimmune disease, including vasculitis and rheumatoid arthritis (RA).[4,5,6] In a previous case-control study on occupational risk factors for GPA, no increased risk of GPA was found for farming, but borderline increased risks were identified for animal keepers (OR 1.8, 95% CI 0.9–3.5).[7]

In our clinic we have observed that animal exposure including contact with horses, either professionally or in leisure activities, seems to be common among patients with GPA, raising the hypothesis of an association between these exposures and the disease. This prompted us to explore environmental exposures with a focus on farming and animal contact as risk factors for GPA.

METHODS

Patients with GPA seen at the Department of Rheumatology, Uppsala University Hospital (the only rheumatology unit serving this population of 350,000 in addition to tertiary referrals from a further 1.7 million people) from January 1, 2011, to December 31, 2018, were consecutively included in the study.

The diagnosis of GPA was validated using the European Medicines Agency algorithm, based on American College of Rheumatology (ACR) and 2012 revised Chapel Hill Consensus Conference (CHCC) criteria.[1]

Information on disease extent, organ involvement, presenting symptoms, and antineutrophil cytoplasmic antibody (ANCA) status was extracted from the medical files. The patients filled in a questionnaire on possible environmental exposures including any animal contact (Supplementary Material, available from the authors on request).

As controls we used 128 patients with RA and 248 population controls,

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The authors declare no conflicts of interest.

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collected from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA-1) study. The EIRA project aims to investigate risk factors for RA, and how such factors may influence disease course. EIRA-1 collected patients from November 1996 to October 2005 and includes questions on domestic animals, pets, and farming.[8]

All controls were matched for sex and age; in order to avoid influence from differences in geographic area of residence, controls were matched for the catchment area of the GPA patients' area of residence at diagnosis.

The GPA questions were grouped according to the exposure reported: farming or domestic pet exposure (including horses but not cattle), respectively. The farming group included both harvesting/crops and cattle, as these entities were not separated in the questionnaires. Because most individuals were exposed to > 1 domestic pet (including horses), the domestic pet group was divided into 4 subgroups and named after the animal to which all individuals in that group were exposed: horse, cat, and dog, and 1 group with individuals exposed to any animal (but not horses).

The patients with GPA were compared to the RA and population controls from the EIRA-1 study, and ORs and 2-sided 95% CIs were calculated for each exposure of interest. A 2-sided 95% CI excluding 1.0 was used to define statistical significance.[9]

Informed consent was obtained from all patients. Ethics approval was received from the Regional Ethics Committee in Uppsala (Dnr 2011/241).

RESULTS

A total of 62 patients with GPA were included in the study, corresponding to a participation rate of 70% (Table 1). Twelve patients died before they could be included (median age at death 77.5 yrs), 5 patients were seen only once at the clinic (second opinion), and 8 were missed. All prompted patients accepted participation. The majority of patients (93%) had ENT and/or lung involvement as presenting symptoms.

GPA was significantly associated with horse exposure, with a 3-fold increased risk compared to RA (OR 3.08, 95% CI 1.34–7.08) and to population controls (OR 2.61, 95% CI 1.29–5.29). Borderline increased risks were found for any animal contact, but exposure to cats and dogs only was not significantly associated with GPA. Farming, including both crops and/or cattle, was borderline significant vs patients with RA but highly significant vs population controls (OR 7.60, 95% CI 3.21–17.93; Table 2).

DISCUSSION

In this case-control study exploring the possible associations of farming and animal contact with GPA, we found a significant 2- to 3-fold increased risk in patients who reported contact with horses compared to the RA and population controls. Moreover, there was a significant association between GPA and farming (cattle and/or crops) as compared to population controls but not compared to patients with RA.

As noted in another study,[10] many patients had been exposed to more than 1 animal. To handle this issue, we analyzed the exposures grouped by the animal all patients had been exposed to. In this comparison, only exposure groups including horses had significantly increased risk. To strengthen this finding, we analyzed cat and dog exposure free from horses and found no increased risk.

A majority of the patients with GPA had respiratory symptoms at diagnosis. As the initial involvement of disease is most often seen in the airways, inhaled antigens have been speculated to play a role in the pathogenesis of GPA.[3] Animal contact, including the environment in stables and barns, animal feeds, and pesticides could all be inhaled triggers, at least in patients with respiratory manifestations.

One of the control groups consisted of well-defined patients with RA. Previously, both GPA and RA have been associated with exposure to silica, whereas other environmental factors are specifically associated with only one of the diseases, such as smoking and RA.[5,11] The present study suggests that exposure to animals—horses in particular—may be a trigger of disease

Table 1. Clinical characteristics of GPA cohort as extracted from medical files, and of the RA and population controls as registered in EIRA-1.

	GPA	RA	Population Controls
Total, n	62	128	248
Age at disease onset, yrs, range (mean)[a]	17–79 (52.8)	19–69 (50.3)	19–70 (52.2)
Sex, female/male	32/30	66/62	116/132
Positive biopsy	51 (82)	–	
ENT involvement	56 (90.3)	–	
Pulmonary involvement	46 (74.3)	–	
Renal involvement	23 (37.1)	–	
ANCA-positive	62 (100)	–	
PR3-ANCA–positive	61 (98.4)	–	
MPO-ANCA–positive	1 (1.6)	–	
RF- and/or ACPA-positive	–	128 (100)	
RF-positive	–	118 (92.2)	
ACPA-positive	–	107 (83.6)	

Values are expressed as n (%) unless otherwise indicated. [a] Age at disease onset for patients with GPA and RA controls; population controls were age-matched to patients with RA. ANCA: antineutrophil cytoplasmic antibody; ACPA: anticitrullinated protein antibodies; EIRA-1: Epidemiological Investigation of Rheumatoid Arthritis study 1; GPA: granulomatosis with polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; RA: rheumatoid arthritis; RF: rheumatoid factor.

Table 2. Association between animal exposures and GPA diagnosis in 62 GPA cases compared to EIRA-1 RA and population controls.

	GPA, n = 62	RA, n = 128	Population Controls, n = 248	GPA vs RA, OR (95% CI)	GPA vs Population Controls, OR (95% CI)
Farm exposure (harvesting and/or cattle)	15 (24.2)	15 (11.7)	10 (4.0)	1.82 (0.84–3.98)	7.60 (3.21–17.93)
Domestic pet exposure	48 (77.4)	83 (64.8)	163 (65.7)	1.86 (0.93–3.73)	1.79 (0.93–3.43)
Horse[a]	15 (24.2)	12 (9.4)	27 (10.9)	3.08 (1.34– 7.08)	2.61 (1.29–5.29)
Cat[b]	33 (53.2)	54 (42.2)	101 (40.7)	1.56 (0.85–2.87)	1.66 (0.95–2.90)
Dog[c]	36 (58.1)	58 (45.3)	113 (45.6)	1.67 (0.91– 3.08)	1.65 (0.94–2.90)
Cat and dog[d]	32 (51.6)	67 (52.3)	127 (51.2)	0.97 (0.52– 1.78)	1.02 (0.58–1.77)

Values are expressed as n (%) unless otherwise indicated. [a] All had exposure to horses, and some to cats and dogs. [b] All had exposure to cats, and some to horses and dogs. [c] All had exposure to dogs, and some to horses and cats. [d] All had exposure to cats and dogs; none had exposure to horses. EIRA-1: Epidemiological Investigation of Rheumatoid Arthritis study 1; GPA: granulomatosis with polyangiitis; RA: rheumatoid arthritis.

specifically in GPA. In contrast, exposure to crops or cattle was associated with GPA only in comparison to population controls, suggesting that this exposure may affect the pathogenesis of several autoimmune diseases. In a previous study from Germany, a significant association between GPA and farming/farm animal exposure was observed, with the strongest association to cattle and pigs. Since most patients had been exposed to more than 1 animal, it was not possible to clearly differentiate between the exposures.[10] A large Swedish case-control study (2288 patients with GPA, taken from the Swedish Inpatient Register, matched with > 22,200 controls from the Swedish Population Register), which investigated potential risk factors for GPA associated with occupational exposures, found no significant association between GPA and farming or occupational animal exposure.[7] However, in this register study, possible animal contact outside of occupational exposures could not be controlled for.

In a study by Lane, *et al*[4] exploring environmental factors for the development of systemic vasculitis, a significant association between farming and GPA was found, but not for eosinophilic GPA (EGPA) or microscopic polyangiitis (MPA). Combining our results, this implies that triggers of autoimmune disease may be distinct not only between vasculitides and arthritic disease but also within the group of ANCA-associated vasculitides. This further supports the hypothesis of an inhaled antigen as a trigger of disease in GPA, characterized by manifestations from the airways, as opposed to MPA, characterized by kidney involvement.

Undoubtedly the present study has limitations, the main one being the limited number of cases. However, only patients fulfilling ACR/CHCC criteria or EMA algorithm for GPA were included. The consecutive inclusion of patients with GPA minimizes the risk of selection bias. Due to hospital organizational issues, patients with severe renal involvement might not have been included. However, this does not seem to have biased the investigated patients, as clinical characteristics were as expected from a GPA cohort. Patients referred to the University Hospital may represent more severe cases, but a majority of patients came from our own catchment areas; only 27% were referrals, reducing the effect of referral bias. All RA controls answered the EIRA-1 questionnaire at diagnosis, whereas due to the consecutive inclusion of the patients with GPA from the clinic, 55% answered the questionnaire at diagnosis and 45% at a later time, possibly introducing a risk of recall bias. However, the question of animal contact ever is not likely to be influenced by time since diagnosis, and the participants were not made aware of our investigational hypothesis. EIRA-1 included questions on pets and domestic animals (as opposed to EIRA-2 starting in 2005), and was therefore chosen as the control population, although the time period does not overlap the GPA patients' inclusion. Although a limitation, we are not aware of changes in the environment or referral practices that would bias the results.

The use of questionnaires is likely to be most efficient in identifying patients with any farm or animal exposure, with minimal risk of underreporting. The questions answered by the patients with GPA were not identical to the questions posed in the EIRA study, but the aim of both questionnaires was to find animal contact ever; hence, the formulation of the questions is not likely to have affected the answers.

In conclusion, our study has identified for the first time, to our knowledge, a significant association between specific animal exposure and GPA. The results also support previous studies reporting association between farming and GPA, underscoring the possibility that these factors may be triggers for GPA.

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