Demographics and environmental factors in a Wegener's granulomatosis cluster

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Wegener's granulomatosis is a multiorgan systemic disease of unknown aetiology, characterised by granulomatous inflammation and vasculitis in small or medium-sized blood vessels. Available evidence suggests a role for genetics, microbial pathogens and environmental exposures in its aetiology.[1] Agents including silica,[2] hydrocarbons,[3] pesticides,[4] fumes[4] and farming[5] have been implicated. We describe the demographic details and environmental exposures of a cluster of patients with Wegener's granulomatosis cases diagnosed in Norfolk, UK. Cluster analysis enables identification of common environmental exposures that may be temporally and spatially related to disease features.

We identified eight patients who were diagnosed with Wegener's granulomatosis between February 2005 and February 2006. All patients fulfilled the 1990 American College of Rheumatology criteria for Wegener's granulomatosis. They were referred to the Norfolk and Norwich University Hospital, Norfolk, UK, which has a catchment area of about 750 000 people. The annual incidence of Wegener's granulomatosis in Norfolk is estimated to be 8.5/million/year in a previous study.[6] A validated questionnaire on environmental exposures, used in a previous study in Norfolk,[5] was administered by an interviewer to all patients.

Table 1 shows the demographic details including estimated age at first symptom (index age) and organ involvement. Two patients were diagnosed with localised Wegener's granulomatosis, as defined by the European Vasculitis Study Group,[7] with involvement of only the upper respiratory tract and negative for classic antineutrophil cytoplasmic antibody (cANCA). The remaining patients were positive for cANCA and had renal involvement (generalised Wegener's granulomatosis). The estimated date of first symptoms (index date) was between 2003 and 2004, and all patients were residents of Norfolk at least a year before.

High farming activity was reported by five patients in the index year, with two patients reporting exposures outside Norfolk, making it the most frequently reported agent. Four patients reported close contact with animals, with three reporting specific exposure to farm animals. Four patients also reported frequent gardening activities. High exposures to dust, construction work and a history of allergy were reported by three patients each. No common factors were identified in occupation, hobbies, infections, and solvent or drug exposure in the index year.

Table 2 shows the association between environmental agents, organ involvement and cANCA status. All patients with localised Wegener's granulomatosis reported no exposure to farming activities in the index year. Five of the remaining six patients with generalised Wegener's granulomatosis reported high exposure to farming.

This concise report on a cluster of Wegener's granulomatosis further supports its association with farming.[5] This study also shows a difference in environmental exposure between localised and generalised Wegener's granulomatosis in a disease cluster, which has not been reported previously. Although it is well known that only 60% of patients with localised Wegener's granulomatosis are positive for cANCA,[8] it is interesting that none of our patients reported exposure to farming in our report. Statistical analysis could not be performed in our study owing to the small number of cases in both groups. Nevertheless, we hypothesise that localised and generalised forms of Wegener's granulomatosis may be

Table 1 Demographics and organ involvement in patients with Wegener's granulomatosis

Sex	Index age (year)	cANCA	Nose/ears	Pulmonary	Renal
Female*	38	−	+	−	−
Male*	52	−	+	−	−
Male	41	+	+	−	+
Female	38	+	+	+	+
Male	47	+	+	+	+
Female	66	+	+	+	+
Male	73	+	+	+	+
Male	47	+	+	+	+

+, positive involvement; −, no involvement; cANCA, classic antineutrophil cytoplasmic antibody. Status confirmed by both immunofluorescence microscopy and ELISA.
*Localised Wegener's granulomatosis.

Table 2 Association of environmental agents according to organ involvement and antineutrophil cytoplasmic antibody status

Item	Farm (n)	High dust (n)	High solvent (n)	Allergy (n)	Gardening (n)	Animals (n)
Renal*	5	2	1	2	3	3
No renal	0	1	0	1	1	1
Pulmonary†	5	2	1	2	4	4
No pulmonary	0	1	0	0	0	0
cANCA	5	2	1	2	3	3
No cANCA	0	1	0	1	1	1

cANCA, circulating anti-neutrophil cytoplasmic antibody.*Haematuria, increased creatinine level or renal biopsy findings, consistent with vasculitis.
†Haemoptysis or chest radiography findings, consistent with vasculitis.

explained by different environmental exposures, and warrant further epidemiological studies.

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MATN3 (matrilin-3) sequence variation (pT303M) is a risk factor for osteoarthritis of the CMC1 joint of the hand, but not for knee osteoarthritis

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Osteoarthritis has a multifactorial aetilogy with a strong genetic component.[1 2] Recently, Stefansson *et al*[3] identified a missense mutation (pT303M) in the *MATN3* (matrilin-3) gene (designated as single-nucleotide polymorphism (SNP)5) in a large cohort of patients from Iceland, which cosegregates with hand osteoarthritis in several families and shows a frequency of approximately 2% in the Icelandic population (relative risk 2.1). Min *et al*[4] were not able to repeat this result in two Dutch cohorts of patients with hand osteoarthritis, but reported association of this SNP with spinal disc degeneration in one of their populations (odds ratio 2.9). In contrast, they found that the A allele of SNP6 (nomenclature as in Stefansson *et al* [3]), a silent base exchange in *MATN3*, is associated with hand osteoarthritis in one of their cohorts (odds ratio = 2.0). Here, we carried out a case–control study of the two polymorphisms for putative association with hand osteoarthritis and knee osteoarthritis in two small cohorts of German patients.

We investigated a sample group of 50 consecutive Caucasian patients (mean age 59.2 years, 84% women) with radiographic and symptomatic hand osteoarthritis of the first carpometacarpal joint (CMC1; late-stage arthritis, EATON stage II–IV), 176 consecutive Caucasian patients (mean age 69.8 years, 79% women) with radiographic and symptomatic knee osteoarthritis (late–stage primary osteoarthritis with complete collapse of the femorotibial joint space) and 356 unrelated Caucasian controls (mean age 38.8 years, 41% women, healthy blood donors recruited in Germany). Patients with CMC1 and knee osteoarthritis were not handled separately. Genotyping of SNP5 and SNP6 in the *MATN3* gene was performed by polymerase chain reaction amplification and subsequent cycle sequencing as described previously.[5]

We analysed the frequency of SNP5 in patients with hand osteoarthritis and in 356 controls and observed a difference in allele frequency ($\chi^2 = 10.84$, $p = 0.001$). The rare T allele of SNP5 was present in 10% of the patients with hand osteoarthritis and in 2.5% of controls (table 1, $\chi^2 = 7.35$, $p = 0.007$). The p value remained significant even after Bonferroni correction for multiple testing. Thus, carriers of the T allele had an increased risk for developing hand osteoarthritis, with an odds ratio of 4.28 (95% CI, 1.18 to 14.8). Interestingly, three of these five patients presented with more scaphotrapezotrapezoidal (STT) joint involvement, a characteristic already described.[7] Thus, we could replicate the results for hand osteoarthritis reported by Stefansson *et al*.[3] Our data support the importance of SNP5 for this specific form of osteoarthritis, but not for knee osteoarthritis (table 1). In contrast with the recent report by Min *et al*,[4] we did not find association of SNP6 with hand osteoarthritis (or knee osteoarthritis; table 1).

The partly contradictory data between the different studies may possibly be due to differences in common diagnostic criteria,[7] or in allele frequencies in the control group.[4] In this respect, it has to be emphasised that our control cohort was randomly selected and is thus not age/sex matched or specifically evaluated for any signs of osteoarthritis. Nevertheless, the fact that the group of patients with knee osteoarthritis (n = 176) exhibit genotype and allele distributions very similar to that of the control cohort (table 1) strongly supports the present association data.

Although the exact role of MATN3 and MATN3 variations in osteoarthritis is still not clear,[8 9] the present data support the importance of variations in the MATN3 gene region for the aetiology of specific forms of osteoarthritis.