
Incidence of granulomatosis with polyangiitis (Wegener's) in Greenland and the Faroe Islands: epidemiology of an ANCA-associated vasculitic syndrome in two ethnically distinct populations in the North Atlantic area

M. Faurischou, M. Helleberg, N. Obel, B. Baslund

¹Department of Infectious Diseases and Rheumatology, The National University Hospital, Rigshospitalet, Copenhagen, Denmark.

Mikkel Faurischou, MD, PhD
Marie Helleberg, MD
Niels Obel, MD, DSci
Bo Baslund, MD, PhD

Please address correspondence and reprint requests to:

Mikkel Faurischou, MD, PhD,
Department of Infectious Diseases and Rheumatology, 4242,
The National University Hospital,
Rigshospitalet,
9 Blegdamsvej,
DK-2100 Copenhagen, Denmark.
E-mail: mikkel@dadlnet.dk

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ABSTRACT

Objective. Previous studies suggest that the incidence of granulomatosis with polyangiitis (Wegener's; GPA) increases along a south-north gradient in the Northern Hemisphere with an incidence of 8.0/million/year reported for the population of Northern Norway. In the present study, we assessed the incidence of GPA in the predominantly Inuit population of Greenland and in the Caucasian population of the Faroe Islands.

Methods. Greenlandic and Faroese patients affected by severe rheumatic diseases are routinely referred to the National University Hospital in Denmark for treatment. By means of the Danish National Hospital Register, we identified all Greenlandic and Faroese patients treated at the hospital under a diagnosis of GPA during 1992-2011. For each patient, the GPA diagnosis was validated by medical files review.

Results. One patient born and living in Greenland and 6 from the Faroe Islands were identified. The incidence of GPA was 1.0/million/year (95% CI 0.02-5.6) in Greenland and 6.4/million/year (95% CI 2.4-14.0) in the Faroe Islands. During the period of study, no cases of GPA occurred among Greenlanders aged 0-44 years, while an incidence of 4.1/million/year (95% CI: 0.1-22.9) was calculated for those aged ≥ 45 years. In the Faroese population, incidences of 1.7/million/year (95% CI 0.04-9.4) and 14.8/million/year (95% CI 4.8-34.6) were calculated for the age-groups 0-44 and ≥ 45 years, respectively.

Conclusions. The occurrence of GPA is lower among Inuit in Greenland than among Caucasians living in the Faroe Islands. This observation demonstrates that the risk of GPA varies across ethnic

groups populating the northernmost regions of the world.

Introduction

Granulomatosis with polyangiitis (Wegener's; GPA) is a rare disorder characterised by inflammatory processes affecting the upper and lower respiratory tract, glomerulonephritis, and the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCA) (1). The pathogenesis of GPA is not well understood. Both infectious agents and occupational exposures have been suggested as risk factors for the disease (2), and a recent study provided evidence of a genetic contribution to disease risk (3). Epidemiologic studies have indicated the existence of a south-north increasing incidence gradient of GPA in the Northern Hemisphere and an inverse gradient in the Southern Hemisphere, raising the possibility that latitude-dependent risk factors may be of pathogenic importance. In the Northern Hemisphere, GPA seems to be more common in Northern Norway, Finland, Southern Sweden, Northern Germany and the United Kingdom than in Spain, with reported annual incidence rates of 8.0/million (4), 9.3/million (5), 9.8/million (6), 6-12/million (7), 11.3/million (8), and 2.9/million (9), respectively. In the Southern Hemisphere, the disease appears to be as common in Australia and New Zealand as in Scandinavia (10, 11), and a higher incidence has been observed in the southern than in the northern part of New Zealand (12). The relative influence of environmental, genetic and other risk factors on the global epidemiology of GPA is unknown. The majority of studies indicating latitudinal trends in disease incidence were conducted in white populations of European descent, and

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investigations of different ethnical groups living along the same latitudes are warranted to assess of the impact of ethnicity and latitude-dependent/environmental factors, respectively, on disease risk.

Greenland is the world's largest non-continental island covering an area of 2.166.086 km² (ice-free area 410.449 km²). The northernmost part of Greenland is 740 kilometres from the North Pole, while the southernmost part lies approximately on the same latitude as Oslo, Norway. The Faroe Islands, which consist of 18 islands covering an area of 1.399 km², are situated halfway between Norway and Island. The latitude of Nuuk, the biggest city of Greenland, is 64°10'N, whereas the latitude of Tórshavn, the major city of the Faroe Islands, is 62°01'N. To shed additional light on the global epidemiology of GPA, we assessed the incidence of the disease in the predominantly Inuit population of Greenland and in the predominantly Caucasian population of the Faroe Islands.

Patients and methods

Greenland and the Faroe Islands are parts of the Kingdom of Denmark, which consists of Denmark proper, Greenland, and the Faroe Islands. For all practical purposes, a Greenlandic-born person can be considered as being equivalent to a person of Inuit ethnicity (13). The vast majority of people inhabiting the Faroe Islands are ethnically Faroese. Historically, the Faroese community is of mixed Scandinavian/British descent, and from a genetic point of view, the Faroese population is highly homogeneous (14). During the period of study, 88–93%, 5–6%, and 0.2–0.3% of people living in the Faroe Islands were born in the Faroe Islands, Denmark, and Greenland, respectively. In the present investigation, we defined a Greenlander as a person born and living in Greenland and a Faroe Islander as a person living in the Faroe Islands. All citizens of the Kingdom of Denmark have unrestricted access to free public health care. People from Greenland and the Faroe Islands are routinely referred to the National University Hospital in Copenhagen if symptoms

suggestive of a severe rheumatic disorder develop.

Every hospital contact to non-psychiatric hospital departments in Denmark initiates a record in the Danish National Hospital Register (15). A record in the register contains dates of admission and discharge, start and end dates of outpatient visits, a primary discharge diagnosis and supplementary diagnoses. Diagnoses were coded according to a Danish version of the International Classification of Diseases, Eight Revision (ICD-8) until the end of 1993 and have been coded according to the ICD-10 thereafter. For Danish and Greenlandic patients, records in the National Hospital Register also contain the personal identification number. This number is unique to each citizen of Denmark and Greenland. Faroese persons are not provided with a Danish personal identification number at birth. However, Faroese persons (and persons of non-Danish citizenship) are assigned a replacement identification number, coded differently than Danish/Greenlandic personal identification numbers, if admitted to a Danish hospital department.

Among patients registered with a diagnosis of GPA in the National Hospital Register between 1992 and 2011, we identified those born in Greenland by linkage with the Danish Civil Registration System. This register system was established in Denmark on April 2, 1968, and in Greenland on May 1, 1972, when all individuals alive and living in Denmark and Greenland were registered. The system contains a range of data on all citizens of Denmark and Greenland, including personal identification number, name, gender, date of birth, place of birth, place of residence, and continuously updated information on vital status (16). To identify patients of Faroese origin, we searched the National Hospital Register for patients treated at the National University Hospital in Copenhagen under a GPA diagnosis and a replacement identification number during 1992–2011. We subsequently identified patients from the Faroe Islands by medical files review. The GPA diagnoses of the identified patients were validated by critical as-

essment of available medical data, and patients who met the ACR classification criteria for GPA were included in the final patient-group (17).

Country-specific population-data for Greenland and The Faroe Islands were collected from national statistical databases at www.stat.gl and www.hagstova.fo, respectively. During 1992–2011 the total number of persons living in Greenland increased from 55.400 to 56.615, and the number of Greenlandic-born persons living in Greenland increased from 47.199 to 50.321. During the same time-period, the population of the Faroe Islands increased from 47.206 to 48.515 persons.

Incidence rates were calculated as the number of incident cases divided by the number of person-years accumulated in the total population, and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of the observed cases.

The study was approved by the Danish Data Protection Agency (journal number 30-0604).

Results

One GPA patient from Greenland and 6 from the Faroe Islands were identified. The Greenlandic patient was of Inuit ethnicity. An additional Greenlandic-born patient (a woman aged 55 years at time of GPA diagnosis in 2011) residing permanently in Denmark was excluded from further analyses, since the person did not develop GPA while living in Greenland. All patients had classic GPA manifestations at time of diagnosis, all were proteinase-3 ANCA-positive, and none presented with symptoms suggestive of other types of ANCA-associated vasculitis (*i.e.* microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis (Churg-Strauss)). A tissue biopsy showing histological changes compatible with GPA was obtained in 6 out of 7 patients. Selected patient characteristics are summarised in Table I. Between 1992 and 2011, the population of persons born and living in Greenland accumulated a total of 987.867 persons-years, and the overall incidence of GPA in this population-group was 1.0/million/year (Table II). No cases of GPA occurred among Greenlanders aged

Table I. Descriptive data for Greenlandic and Faroese patients diagnosed with granulomatosis with polyangiitis (Wegener's) during 1992–2011.

Patient	Year of diagnosis	Age at diagnosis	Sex	Area of residence at disease onset	Disease manifestations at diagnosis	ANCA-specificity
1	1992	70	M	Greenland	ENT, lung	PR3-ANCA
2	1993	54	M	Faroe Islands	ENT, lung, joints, renal	PR3-ANCA
3	1993	54	M	Faroe Islands	Eye, ENT	PR3-ANCA
4	1994	41	M	Faroe Islands	ENT, lung, joints, renal	PR3-ANCA
5	1996	50	F	Faroe Islands	Eye, ENT, joints, skin	PR3-ANCA
6	1998	67	F	Faroe Islands	Joints, renal	PR3-ANCA
7	2005	58	M	Faroe Islands	ENT, joints, skin, renal	PR3-ANCA

ANCA: Anti-neutrophil cytoplasmic antibody; PR3: Proteinase-3; ENT: ear, nose, and throat; F: Female; M: Male.

Table II. Incidence rates of granulomatosis with polyangiitis (Wegeners) in Greenland and the Faroe Islands during 1992–2011.

	Number of cases	Mean annual incidence per million	95% confidence interval
Greenland*			
Overall	1	1.0	0.02–5.6
Age 0–44 years	0	0.0	0.0–4.9
Age ≥45 years	1	4.1	0.1–22.9
Faroe Islands			
Overall	6	6.4	2.4–14.0
Age 0–44 years	1	1.7	0.04–9.4
Age ≥45 years	5	14.8	4.8–34.6

*Only persons born and living in Greenland were included in the analyses.

0–44 years during the period of study. Among persons aged ≥45 years, the incidence of GPA was 4.1/million/year. The six Faroese cases of GPA were diagnosed during a total of 932.220 person-years, corresponding to an incidence of GPA of 6.4/million/year in the Faroe Islands. The occurrence of the disease was 8.7 times higher among Faroe Islanders aged ≥45 years than among persons of younger ages (Table II).

Discussion

The present study adds to current insight into the global epidemiology of GPA by providing data on the incidence of the disease in two ethnically distinct populations in the North Atlantic area. To our knowledge, this is the first investigation of the epidemiology of an ANCA-associated vasculitic syndrome among persons of Inuit ethnicity.

Koldingsnes and Nossent calculated an incidence of GPA of 8.0/million/year for the population of Northern Norway using a methodological approach, which is comparable to ours (register-based case retrieval followed by case validation by medical files review) (4). We found a much lower incidence of GPA among Greenlanders, while the incidence of GPA in the Faroe Islands seems to be of the same magnitude as that in Northern Norway. Together, the two investigations demonstrate that the incidence of GPA varies across ethnic groups populating the northernmost regions of the world with a higher occurrence of the disease among Caucasians than among persons of Inuit ethnicity. The importance of ethnicity-dependent factors for the disease risk in GPA was previously suggested by findings from New Zealand, where GPA seems

to be more common among Caucasians than among persons of Maori or Asian descent (12). Moreover, in a study by Mahr and co-workers, the prevalence of ANCA-associated vasculitides and polyarteritis nodosa combined was found to be two times higher among subjects of European ancestry than among those of Non-European ancestry in a suburb of Paris (France) (18). Thus, our study adds to a growing amount of data pointing towards a significant impact of ethnic/genetic factors on the risk of developing GPA and other primary vasculitides (3, 4, 12, 18, 19). Of note, however, both genetic and non-genetic risk factors are likely to be of importance for the global epidemiology of the ANCA-associated vasculitides. Comparative analyses of the incidence of ANCA-associated vasculitides in Tromsø (Norway), Norwich (England), and Lugo (Spain) revealed regional variations in the occurrence of these syndromes, with a higher incidence of GPA in England and Norway than in Spain, a higher incidence of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in England than in Norway and Spain, and an inverse relation between the incidence of GPA and that of microscopic polyangiitis across the three regions (20, 21). These findings suggest that environmental triggers might also influence the geo-epidemiology of the different types of ANCA-associated vasculitis. Though based on few incident cases, our analyses indicate a higher occurrence of GPA among Greenlandic and Faroese persons aged ≥45 years than among those of younger ages. As in previously described European populations (4, 5, 8, 9), the risk of GPA therefore seems to increase with age in these communities.

The present investigation has both strengths and weaknesses. The completeness of the Danish National Hospital Register allowed for complete tracking of Greenlandic and Faroese GPA patients treated at the National University Hospital in Denmark during the period of study, and the data kept by Statistics Greenland and Statistics Faroe Islands enabled us to define the size of the denominator popula-

tions with great precision. As would be expected from the small size of the Greenlandic and Faroese communities and the rarity of GPA in other population-groups, we identified very few GPA patients, and this resulted in relatively wide 95% CIs for the calculated incidence rates. Most of the observed cases occurred in the 1990s. Since no changes in referral practices were implemented during the period of study, this clustering of cases is likely to be incidental. Due to the challenging geographic conditions of Greenland and the life-threatening features of GPA in its systemic form, it is possible that some GPA patients living in remote areas of the country may have died from the disease before reaching specialised hospital centres in Denmark for diagnosis and treatment. Consequently, it cannot be ruled out that the calculated incidence rate for the Greenlandic population was to some extent influenced by incomplete case capture. However, since all persons living in the Kingdom of Denmark are covered by a free public health care system and are entitled to free transport to tertiary care centres if specialised medical care is needed, the number of Greenlandic GPA patients not diagnosed for logistic reasons is likely to be very limited.

In summary, we observed a lower occurrence of GPA in the predominantly Inuit population of persons born and living in Greenland than in the predominantly Caucasian population of the Faroe Islands. This finding demonstrates that the incidence of GPA varies across ethnic groups populating the North Atlantic area. Our study thus

provides further data suggesting a significant influence of ethnicity-dependent factors on the global epidemiology of the disease.

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