Concise report

Impact of pre-existing co-morbidities on mortality in granulomatosis with polyangiitis: a cohort study

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Abstract

Objective. To assess the impact of pre-existing co-morbidities on mortality among patients affected by granulomatosis with polyangiitis (GPA).

Methods. By means of the Danish National Hospital Register, we identified a cohort of patients hospitalized for GPA during 1994-2010 (n = 308). The burden of pre-existing co-morbidities among the patients was quantified according to the Charlson Comorbidity Index (CCI). Each patient was matched with five age- and gender-matched population controls with no pre-existing co-morbidities captured by the CCI (CCI score = 0). The study subjects were followed throughout 2010. Cox regression analyses were used to calculate mortality rate ratios (MRRs).

Results. The median duration of follow-up in the GPA cohort was 5.8 years (interquartile range 2.3-10.0). Compared with their matched population controls, the MRR for patients presenting with a CCI score of 0 (n = 246) was 3.9 (95% CI 2.0, 7.5) during years 0-2 and 1.4 (95% CI 0.9, 2.0) from the second year of follow-up onwards. The corresponding MRRs were 13.3 (95% CI 5.8, 31) and 1.9 (95% CI 1.1, 3.6) for patients with a CCI score >1 (n = 62). In a direct comparison, GPA patients with a CCI score >1 were found to have significantly higher mortality than GPA patients with a CCI score of 0 during years 0-2 [adjusted MRR 3.4 (95% CI 1.6, 7.0)] but not after >2 years of follow-up [adjusted MRR 1.3 (95% CI 0.7, 2.6)].

Conclusion. During early follow-up periods, the mortality among GPA patients with pre-existing co-morbidities is markedly higher than that among GPA patients with no pre-existing illnesses. Our analyses identify an increased CCI score for pre-existing co-morbidities as an important risk factor for a fatal outcome in GPA.

Key words: granulomatosis with polyangiitis, vasculitis, co-morbidity, Charlson, mortality

Introduction

Granulomatosis with polyangiitis (GPA) is a potentially lethal vasculitic syndrome [1]. Cyclophosphamide-based treatment regimens were introduced >30 years ago and have improved the prognosis in GPA [2, 3]. However, the disease remains associated with a considerable risk of organ damage and with increased mortality [4, 5].

Several investigators have analysed the impact on mortality of vasculitis-related and demographic variables registered at the time of diagnosis among patients with GPA [6-10]. In contrast, little is known about the influence on mortality of co-morbidities acquired by GPA patients before the onset of vasculitis. Ofer-Shiber et al. [11] identified high levels of pre-existing co-morbidity as a risk...
factor for death in a small cohort of 16 GPA patients and 14 patients with other ANCA-associated vasculitides. To our knowledge, however, the mortality risk associated with pre-existing co-morbidities among GPA patients has not been analysed in large-scale epidemiological studies.

The aim of the present nationwide cohort study was to assess the extent to which the early and late mortality of GPA patients with pre-existing co-morbidities differs from that of patients with no pre-existing co-morbidities.

Methods

GPA cohort

The Danish National Hospital Register (NHR) was founded in 1977 and contains records on admissions to non-psychiatric hospital departments in Denmark with complete coverage [12]. Information on outpatient hospital contacts has been included since 1995. Every hospital visit initiates a record, which is marked by the patient’s personal identification number (a unique number assigned to each citizen of Denmark at birth or immigration) and includes dates of admission and discharge, hospital and department codes, start and end dates of outpatient visits, a primary discharge diagnosis and supplementary diagnoses. The diagnoses were coded according to a Danish version of the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and have been coded according to the ICD-10 thereafter. The study was approved by the Danish Data Protection Agency (jr. no. 30-0604) and the Danish National Board of Health (jr. no. 3-3013-856/1).

In the NHR, we identified all patients who were registered with a first-time diagnosis of GPA (ICD-8 code 446.29; ICD-10 code M31.3) during 1994–2010, and experienced at least two hospitalizations (both inpatient hospital admissions and outpatient contacts were counted) for GPA at any department of rheumatology in Denmark during this period. The second of these hospitalizations was defined as the study index date. Patients were not considered eligible if the time between the first-ever hospitalization for GPA and the index date was $\geq 1.5$ years.

Validation of GPA diagnoses in the NHR

The validity of GPA diagnoses in the NHR was investigated by a medical files review. For practical reasons, we based this investigation on patients hospitalized for GPA at rheumatology departments in the capital region of Denmark.

Among the identified cases, we performed a search for the medical records of the 75 most recently registered patients. Available medical charts were reviewed and patients who met the ACR classification criteria for GPA [13] were considered to be registered correctly.

We were able to retrieve the medical files for all patients selected for case validation. Sixty-eight of these were assessed to be registered appropriately, yielding a positive predictive value (PPV) of 0.91 (95% CI 0.82, 0.96; Clopper-Pearson binomial CI) for GPA diagnoses identified in the NHR by means of our search strategy.

Comparison cohort

The Civil Registration System contains a range of data on each citizen of Denmark, including personal identification number, name, gender, date of birth and continuously updated information on migrations and vital status [14]. For each GPA patient, we used the Civil Registration System and the NHR to identify five random Danish citizens fulfilling the following requirements: had the same date of birth and gender as the GPA patient; were alive, not diagnosed with GPA and living in Denmark at the index date of the patient; and presented with a Charlson Comorbidity Index (CCI) score of 0 (calculated as outlined below). The population controls were assigned the same index date as the GPA patients to whom they were matched.

CCI

The CCI provides a co-morbidity score based on selected diseases [15]. The index was developed as a scoring system with the ability to predict mortality in longitudinal studies. It has been adapted for use with register-derived data [16]. In the CCI, a score of 1–6 is assigned to a range of illnesses depending on the strength of their association with mortality (myocardial infarction, 1 point; congestive heart failure, 1 point; peripheral vascular disease, 1 point; cerebrovascular disease, 1 point; dementia, 1 point; chronic pulmonary disease, 1 point; connective tissue disease, 1 point; ulcer disease, 1 point; mild liver disease, 1 point; diabetes, 1 point; hemiplegia, 2 points; moderate or severe renal disease, 2 points; diabetes with end-organ damage, 2 points; any tumour, 2 points; leukaemia, 2 points; lymphoma, 2 points; moderate or severe liver disease, 3 points; metastatic solid tumour, 6 points; AIDS, 6 points).

We computed a CCI score for all study subjects based on their complete history in the NHR. In this register, PPVs of 82–100% were previously reported for the ICD-10 codes used to calculate the CCI score [17]. A list of the analysed ICD-8 and ICD-10 codes is provided in supplementary Table S1, available at Rheumatology Online. To avoid the possibility of mixing causality, ICD-8/ICD-10 codes listed under the CCI category connective tissue disease were not included in our computations.

The GPA patients were followed for hospitalizations under relevant ICD-8/ICD-10 codes until 2 years before the index date. Co-morbidities registered thereafter were not analysed to reduce the risk of including inflammatory manifestations or sequelae of yet undiagnosed GPA among the counted co-morbidities. The population controls were tracked for co-morbidities until the same date.

Deaths and emigrations

Data on deaths and emigrations were obtained from the Danish Civil Registration System.
Results

The GPA cohort comprised 308 patients (155 women) and 1540 age- and gender-matched persons were included in the comparison cohort. The median age at the index date was 56 years (range 15–85). In the GPA cohort, the median time from first-ever hospital contact for GPA to the index date was 0.1 years [interquartile range (IQR) 0.05–0.2] and the median duration of follow-up was 5.8 years (IQR 2.3–10.0). Only seven patients never experienced inpatient hospitalisation under a primary or supplementary diagnosis of GPA. A total of 80 patients and 217 controls died during the period of observation. No study subjects were lost to follow-up.

Pre-existing co-morbidities were present in 62 GPA patients (co-morbidities by CCI category: myocardial infarction, 7; congestive heart failure, 6; peripheral vascular disease, 4; cerebrovascular disease, 13; chronic pulmonary disease, 15; ulcer disease, 6; mild liver disease, 5; diabetes, 6; moderate or severe renal disease, 4; diabetes with end-organ damage, 3; any tumour, 16; lymphoma, 2; moderate or severe liver disease, 1; metastatic solid tumour, 2). Among these patients, the median CCI score for pre-existing co-morbidities was 2 (range 1–8).

Within the first 2 years of observation, GPA patients presenting with a CCI score of 0 had an MRR of 3.9 (95% CI 2.0, 7.5) compared with their matched population controls (Table 1). During this time, the corresponding MRR was 13.3 (95% CI 5.8–31) among GPA patients with a CCI score ≥ 1. Beyond the second year of follow-up, the MRRs were 1.4 (95% CI 0.9, 2.0) and 1.9 (95% CI 1.1, 3.6) for these groups, respectively.

To examine whether the impact of co-morbidities on mortality varies with age and gender in GPA, we performed analyses stratified according to these variables (Table 1). During the first 2 years, MRRs for patients versus population controls were 3.7–4.6 times higher among GPA patients with a CCI score ≥ 1 than among GPA patients with a CCI score of 0 across gender groups and age strata. During later follow-up, we observed less pronounced differences in age- and gender-specific MRRs between these subgroups of patients (Table 1).

In a direct comparison, the mortality among GPA patients with a CCI score ≥ 1 was found to be significantly higher than that among GPA patients with a CCI score of 0 during the first 2 years of follow-up, but not from the second year onwards (Table 2).

Discussion

The present investigation constitutes the first nationwide cohort study of the mortality risk associated with...
pre-existing co-morbidities in GPA. We used data from national registries to establish a cohort of GPA patients presenting with a CCI score of 0 and to compare the mortality among those patients with that among population controls with a similar CCI score. These analyses, which provide a relatively pure estimate of the mortality attributable to GPA, demonstrated excess mortality during early follow-up periods among otherwise healthy GPA patients. We also used register-derived data to construct a cohort of GPA patients presenting with one or more chronic diseases captured by the CCI. These patients were found to have substantially higher mortality than GPA patients with no pre-existing co-morbidities during the first 2 years of observation. Thus our findings underscore the life-threatening disease features of GPA and identify an increased CCI score for pre-existing co-morbidities as an important contributing risk factor for death among GPA patients.

Our investigation has strengths and limitations. We based our analyses on the NHR, which collects data on all hospitalizations in Denmark, and the Danish Civil Registration System, which contains information on migrations and deaths among Danish citizens with complete coverage. In the NHR, high PPVs were previously reported for hospital discharge diagnoses used to calculate the CCI score [17], and our study demonstrates a high PPV for GPA diagnoses identified in the register by means of the applied search strategy.

Some of the registered co-morbidities in the GPA cohort might have represented misclassified manifestations of vasculitis. However, co-morbidities registered <2 years before the index date were not counted, we refrained from analysing diagnoses listed under the CCI category connective tissue disease, and we did not include in our cohort patients for whom time from first-ever hospitalization for GPA to the index date was  stage of disease features. Thus measures were taken to reduce the risk of unintended inclusion of vasculitis manifestations in the co-morbidity index score and diagnostic misclassification is unlikely to have significantly biased the analyses stratified according to CCI score.

We only searched the NHR for GPA patients treated at departments of rheumatology. Consequently, persons who died from GPA without receiving treatment at such departments (e.g. patients treated at nephrology units only) were not included in our cohort. Since severe renal disease is a risk factor for a fatal outcome in GPA [18, 19], the true short- and long-term mortality of Danish GPA patients relative to that of population controls with a CCI score of 0 is likely to be higher than observed in our study. There is, however, no reason to assume that the observed effect of pre-existing co-morbidities on relative risk of death was substantially influenced by selection bias, since the risk of death associated with an increased CCI score for pre-existing illnesses is unlikely to differ between GPA patients treated by rheumatologists and those treated exclusively by doctors of other medical specialties. Our analyses did not reveal significantly higher mortality among GPA patients with a CCI score ≥ 1 than among those with a CCI score of 0 beyond the second year of observation, but we cannot rule out that a greater impact of pre-existing co-morbidities on long-term mortality would be detectable in analyses based on longer follow-up.

In summary, the present study demonstrates markedly higher mortality among GPA patients with pre-existing co-morbidities than among GPA patients with no pre-existing illnesses during early follow-up periods. Thus our findings suggest that priority should be given to administering the optimal therapy for co-morbidities in patients with GPA. We also demonstrate excess mortality during early follow-up among GPA patients with no pre-existing co-morbidities. This observation highlights the need for better treatment options for patients affected by the syndrome.

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Supplementary Data
Supplementary data are available at Rheumatology Online.

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