Giant Cell Arteritis and Mortality

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Background. Giant cell arteritis (GCA) is a systemic vasculitis of elderly individuals associated with significant morbidity, including blindness, stroke, and myocardial infarction. Previous studies have investigated whether GCA is associated with increased mortality, with conflicting results. The objective of this study is to determine whether GCA, is associated with increased mortality.

Methods. Forty-four cases with GCA were identified from the University of Utah Health Sciences Center, the major tertiary care center for the Intermountain West. The Utah Population Database, a unique biomedical information resource, selected cases and age- and gender-matched controls. Cases were defined as patients with a temporal artery biopsy-proven diagnosis of GCA (international classification of diseases [ICD]-9 code 446.5) between 1991 and 2005. Exclusion criteria included a negative biopsy, alternative diagnoses, or insufficient clinical data. For each of the 44 cases, 100 controls were identified; thus, 4,400 controls were included in the data analysis. Median survival time and 5-year cumulative survival were measured for cases and controls.

Results. The median survival time for the 44 GCA cases was 1,357 days (3.71 years) after diagnosis compared with 3,044 days (8.34 years) for the 4,400 controls ($p = 0.04$). Five-year cumulative survival was 67% for the control group versus 35% for the cases ($p < .001$). Survival rates for cases and controls converged at approximately 11.12 years.

Conclusions. Patients with GCA were more likely than age- and gender-matched controls to die within the first 5 years following diagnosis.

Key Words: Giant cell arteritis—Vasculitis—Temporal arteritis—Mortality—Utah population database.

G IANT cell arteritis (GCA) is a systemic vasculitis of elderly individuals associated with significant morbidity. GCA can result in vision loss, peripheral neuropathies, scalp necrosis, altered mental status, congestive heart failure, myocardial infraction, aortitis, aortic aneurysm, and stroke (1–15). Mortality among patients with GCA may be due to cerebral arteritis, coronary arteritis, aortic aneurysm rupture, and thromboembolic events (16–18).

Previous studies have attempted to address whether GCA is associated with increased mortality, with conflicting results (Table 1). Some studies have concluded that GCA has no effect on mortality (8,18–20,22–24,27,29,30,32), whereas others suggest that GCA is associated with short- or long-term increases in mortality (21,25,26,28,31). Many of these studies had limitations such as a small sample size (19,22,25) or inclusion of cases with diagnoses not confirmed by biopsy (8,19,22,24,26,27,32).

The purpose of this study was to rigorously evaluate the effect of GCA on mortality by conducting an analysis that included only biopsy-proven cases. Rather than relying on life tables or standardized mortality ratios, we identified 100 controls for each case matched by birth year, gender, and birthplace geography.

METHODS

This retrospective cohort study was approved by the University of Utah Institutional Review Board. Our investigation utilized data from the Utah Population Database (UPDB), a unique biomedical and health-related information source which collects all coded medical diagnoses at the University of Utah Health Sciences Center (including inpatients and outpatients), all death certificates and the majority of birth certificates for the state of Utah (33). We searched the UPDB for patients coded for GCA (international classification of diseases [ICD]-9 code 446.5) between 1991 and 2005. In addition, medical records were reviewed for inclusion and exclusion criteria of all potential study subjects initially identified by the UPDB. A subject was included only if his or her chart contained a report of a positive superficial temporal artery biopsy. Potential subjects were excluded if they were found to have a negative biopsy, an alternative diagnosis, or insufficient clinical data. Collected data also included birth date, diagnosis date, gender, date of death or last follow-up, steroid use, diagnosis of polymyalgia rheumatica (PMR), and ophthalmic findings.

Age- and gender-matched controls for each subject were identified within the UPDB. Controls were also matched to cases by geographic location. Controls were included only if they had a last follow-up date at or beyond the date of disease onset for the case. A random number generator was used to select 100 controls for each case. No control was used for more than one case. Due to the advanced age of one case, the matching birth year had to be expanded by ±2.5 years to identify 100 controls.

Table 1. Comparative Analysis of Giant Cell Arteritis Mortality Studies to Date

Study	Year	Number of Patients	Percent Biopsy Proven	Primary Method of Analysis	Unit Time	Findings
Hauser and colleagues (19)	1971	19	63	Life table	y	No effect
Huston and colleagues (8)	1978	42	90	Kaplan-Meier	mo	No effect
Jonasson and colleagues (20)	1979	136	100	Standardized mortality ratio	mo	No effect
Graham and colleagues (21)	1981	90	100	Life table	mo	Increased mortality in women
Chuang and colleagues (22)	1982	15	93	Kaplan-Meier	mo	No effect
Gouet and colleagues (23)	1985	87	100	Life table	y	No effect
Andersson and colleagues (24)	1986	90	72	Standardized mortality ratio	mo	Increased 5-y survival, no effect at 10 and 15 y
Nordborg and Bengtsson (18)	1989	284	100	Standardized mortality ratio	mo	No effect
Bisgård and colleagues (25)	1991	34	100	Standardized mortality ratio	y	Increased mortality
Nesher and colleagues (26)	1994	43	91	Standardized mortality ratio	mo	Increased mortality
Matteson and colleagues (27)	1996	205	Not reported (<100)	Standardized mortality ratio	d	No effect
García-Porrúa and colleagues (28)	1996	54	100	Standardized mortality ratio	mo	Increased mortality at 5 y, no effect at 10 y
González-Gay and colleagues (29)	1997	109	100	Standardized mortality ratio	mo	No effect
Gran and colleagues (30)	2001	42	100	Cox proportional hazard	mo	No effect
Uddhammar and colleagues (31)	2002	136	100	Standardized mortality ratio	d	Increased mortality in women
Salvarani and colleagues (32)	2004	173	87	Kaplan-Meier	d	No effect
Crow and colleagues	2007	44	100	Kaplan-Meier	d	Increased mortality at 5 y

Note: d = days; mo = months; y = years.

A biostatistician (S.C.A.) analyzed the data using the Kaplan-Meier (product limit) method with a post hoc log-rank comparison of the survival of cases and controls. SPSS 15.0 for Windows© (SPSS Inc., Chicago, IL) was used for the analysis. For statistical significance, α was set at 0.05. Five-year survival curves, median survival times, and 95% confidence intervals were calculated for each group. Survival was measured in days to maximize the sensitivity of the analysis.

RESULTS

Two hundred eighty-eight subjects were initially identified by the UPDB as having an ICD-9 diagnosis of 446.5. After medical record review, GCA diagnosis was confirmed in 44 subjects. Clinical and demographic data for these 44 cases are summarized in Table 2. From 236,217 UPDB-identified potential controls, 4,400 were randomly selected.

At the time of this analysis, 21 of the 44 patients were deceased. Analysis of cause of death information revealed that none of the patients had died as a direct result of GCA. Seven patients had died as a result of treatment (gastrointestinal hemorrhage, pneumonia, urinary tract infection, sepsis), eight patients had died as a result of diseases unrelated to GCA or its treatment, and for six patients there were insufficient data to make a determination as to the cause of death and its relationship to GCA or its treatment.

The median survival time for the 44 GCA cases was 1,357 days (3.71 years) after diagnosis, compared with 3,044 days (8.34 years) for the controls ($p = .04$). The 5-year cumulative survival for the 44 GCA cases was 35%, versus a 5-year survival of 67% for the 4,400 control subjects ($p < .001$; Figure 1). The cumulative survival in the control group reached 35% at approximately 11.12 years.

DISCUSSION

Our results indicate that a diagnosis of GCA is significantly associated with reduced 5-year survival. The survival rates for cases and controls converge at 11.12 years, suggesting that the adverse affect on survival is present only in the years immediately following diagnosis. At this time survival data beyond this point are limited, making further inferences difficult.

When compared with clinical and demographic features described in the literature, the ages of our 44 GCA cases are representative of other study populations with the disease. Although only nine of our 44 patients (20.5%) had a concurrent diagnosis of PMR, many more had symptoms that closely resembled those of PMR. Thus, PMR prevalence in our subjects is consistent with previous reports. The ratio of females to males in our study was 6.3:1, whereas most studies have found this ratio to be closer to 2:1 (6,12). We found that almost 55% of our patients had vision loss, more than other studies have reported, because as ophthalmologists we emphasize vision loss assessment. Another study has reported that GCA patients with vision loss have a reduced survival rate when compared with GCA patients with unchanged vision (34). Therefore, patients who present with new visual symptoms should receive especially careful and regular follow-up assessment and care.

Because this study is a retrospective chart review, it lacks uniformity of history taking, chart information, and treatment. An additional limitation is the variability of follow-up time and attrition during the study. Information regarding treatment regimens and duration, as well as presence or absence of standard cardiovascular risk factors, was not consistently available. Nonetheless, this investigation represents a unique approach to the assessment of GCA-associated

Table 2. Clinical and Demographic Data for Giant Cell Arteritis
Study Subjects

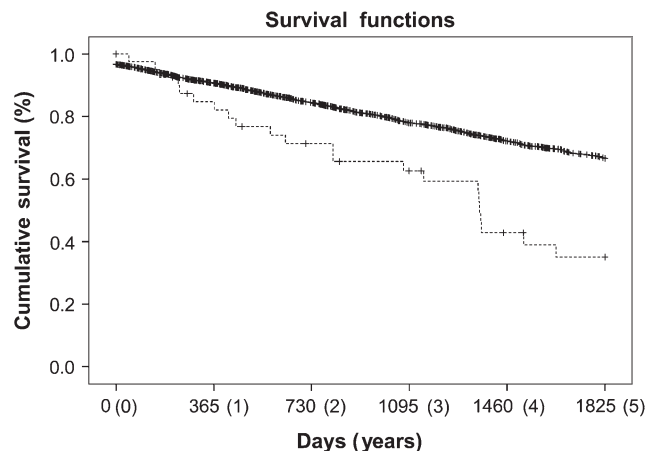| Total number of patients	44
Mean age at diagnosis	76.7 y
Age range at diagnosis	57–93 y
Females	38 (86.4%)
Males	6 (13.6%)
Female:male ratio	6.3:1
Living	23 (52.3%)
Deceased	21 (47.7%)
Polymyalgia rheumatica diagnosis	9 (20.5%)
Vision loss	24 (54.5%)

Figure 1. Kaplan-Meier analysis to compare the cumulative survival curves of 44 biopsy-proven giant cell arteritis (GCA) patients (dashed line) to 4,400 controls (solid line). One-hundred controls were randomly selected for each of the 44 GCA patients after being matched by birth year and gender. The 5-year survival of GCA patients is significantly reduced compared with that of the control group ($p < .001$).

mortality in that we have compared our GCA cases with controls matched by age, gender, and geography.

In order to optimally understand our results in the context of previous studies, it is important to compare the statistical methods previously employed. A number of prior studies relied on life tables, which demographers construct by defining an age interval (generally 1 year) and then comparing the number of subjects alive at the beginning of the interval with the number of subjects alive at the interval's end. Age-specific mortality rates are calculated if the subjects are divided by age. The 1-year time intervals typically used for life tables have limited sensitivity in an elderly population; for example, the life expectancy of an 80-year-old individual may differ significantly from that of an 80.5-year-old. In addition, the age-specific rates in the standard population are based on empirical observations, which will show random fluctuation (35). We have addressed the limitations of using life tables by defining a cohort of 100 control subjects for each study subject and then performing a survival analysis of the two groups.

Some previous studies attempted to integrate both early and late effects on longevity, to detect an initial negative effect on survival, or to identify a return to normal age-related mortality rates (23,24,28,29). One research team initially observed that patients with GCA had a significantly *reduced* mortality when compared with the expected mortality rate, but this finding was not observed with long-term follow-up (24,36). We found that the diagnosis of GCA significantly affects the 5-year survival rate; but by 11.12 years the mortality rates of the groups converge, suggesting that the negative impact of GCA on survival is eventually lost. Our statistical methodology enabled us to demonstrate both the initial, negative effect on longevity and the loss of this effect over time.

Although our results indicate that the 5-year survival of GCA patients is significantly less than that of a control group, our results do not address whether GCA itself or consequences of treatment of GCA is directly responsible for this increase in mortality. Elderly individuals, such as those in our study population, often have comorbidities that affect longevity. Furthermore, although GCA typically runs a self-limited course of 1–2 years, some patients experience spontaneous relapses during or after the 5 years following diagnosis (6,8,12,37). One may hypothesize that because

the disease is more likely to be active during the first 5 years than during the subsequent 6–10 years, mortality from GCA and its treatment is greatest during the first 5 years following diagnosis. Based on our results, patients who survive the first 5 years after diagnosis may have a mortality rate that reflects that of other elderly patients in the general population (38–40).

We recommend that further studies be directed at identifying risk factors for early death after a diagnosis of GCA. Specific attention should be given to known vascular disorders, cardiac disease, and large vessel disease. Furthermore, genetic testing has proven to be useful in diagnosis or treatment of ophthalmic as well as vascular disorders, and development of such tests in the future may enhance our ability to identify risk factors for increased GCA-associated morbidity and mortality (41–44). Perhaps by identifying those patients at risk for early death, we can intervene before life-threatening complications arise.

to the work and has obtained written consent from all contributors who are not authors and are listed as follows:

Study concept and design: R.W.C., B.J.K., J.E.A.W., and K.B.D.

Acquisition of data: R.W.C., B.J.K., J.E.A.W., K.Z., and K.B.D.

Analysis and interpretation of data: R.W.C., B.J.K., J.E.A.W., S.C.A., K.B.D., and S.S.

Preparation of the manuscript: R.W.C., B.J.K., J.E.A.W., S.C.A., K.Z., S.S., and K.B.D.

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