Racial Differences in the Prevalence of Monoclonal Gammopathy in a Community-based Sample of the Elderly

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PURPOSE: To determine if there is an increased prevalence of monoclonal gammopathy in elderly blacks compared with whites, analogous to the difference in incidence of multiple myeloma reported for the two racial groups and to confirm age and gender relationships.

PATIENTS AND METHODS: Subjects were from the Duke Established Populations for the Epidemiologic Study of the Elderly, selected on the basis of stratified random household sampling. Blacks were oversampled to allow for increased statistical precision in racial comparisons. In all, 1,732 subjects (aged >70 years) consented to blood drawing and constitute the sample for this study. Monoclonal immunoglobulins were determined by agarose gel electrophoresis and immunofixation.

RESULTS: One hundred six subjects (6.1%) had a monoclonal gammopathy. There was a greater than twofold difference in prevalence between blacks (8.4%) and whites (3.8%) ($P < 0.001$); monoclonal gammopathy prevalence increased with age, and was greater in men than women. Those with monoclonal gammopathy did not differ from those without in socioeconomic status, urban/rural residence, or education. The presence of monoclonal gammopathy was not associated with any specific diseases nor with impaired functional status. There was a slight increase in serum creatinine levels and decrease in hemoglobin and albumin levels in patients with monoclonal gammopathy, but no difference in interleukin-6 (IL-6) levels. Moreover, IL-6 levels were not correlated significantly with the level of monoclonal protein.

CONCLUSION: Prevalence of monoclonal gammopathy is significantly greater among blacks than whites in a community-based sample, in approximately the same ratio that multiple myeloma has been reported in the two groups. Given the absence of correlation with environmental factors, there may be a biological racial difference in susceptibility to an early event in the carcinogenic process leading to multiple myeloma. **Am J Med. 1998;104:439–444.** ©1998 by Excerpta Medica, Inc.

The monoclonal gammopathies, or presence of a monoclonal immunoglobulin protein in the plasma, include a spectrum of disorders from the full-blown disease multiple myeloma, to monoclonal gammopathy of unknown significance (MGUS), where the protein is seen in the absence of associated disease (1–3). Both myeloma and its benign, sometimes precursor phenomenon, MGUS, increase strikingly with age (4–8), although the frequency of MGUS is approximately 200 times greater than that of multiple myeloma (9). MGUS is also more common in men than women (3,4). The initial description of MGUS, based on a sample of about 7,000 people in Malmo, Sweden, reported a prevalence of 2% in subjects between age 70 and 79, and 5.7% in those over 80 years of age (10). This study and the only other population-based survey, in Olmstead County, Minnesota, showing a similar prevalence were of entirely Caucasian populations (11).

The incidence of multiple myeloma varies by race, being greater in blacks than whites, and least in Asians (8,12–14). Because of these differences, determining whether monoclonal gammopathies also show the same racial variation would suggest that the etiologic event in the phenomenon occurs at an early stage ("first hit") in the carcinogenic process, rather than at a subsequent stage. Our previous study of a retirement community/clinic-based sample indicated that the prevalence of monoclonal gammopathies is much lower in Japanese than Caucasian patients (15). Two previous studies conducted in selected samples of male veterans in whom serum protein electrophoresis had been requested for clinical purposes suggested that the prevalence of monoclonal gammopathies is greater in blacks than whites (16,17). However, no population-based study that includes substantial numbers of black subjects has been conducted.

To determine the comparative prevalence of monoclonal gammopathies in blacks and whites, we initiated a

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study utilizing more than 1,700 subjects in a population-based setting that had been specifically designed for racial comparisons (18,19). Because socioeconomic status and environmental exposures, largely through occupation, have been suggested as possible etiologic factors, we also assessed these characteristics (20–22).

METHODS

Subjects

Subjects were from the Duke Established Populations for the Epidemiologic Study of the Elderly (18). The general characteristics of the survey population have been described previously (19). Briefly, from 1986 to 1987, the Duke study enrolled 4,164 subjects aged 65 years and older, selected on the basis of stratified random household sampling in a five-county area, Durham, North Carolina (an urban county), and four adjacent rural counties. The sample was selected specifically to allow for racial comparison. Blacks were oversampled, yielding 54% of those participating. All but 26 of the remaining subjects were white. The initial in-person survey included extensive information on cognitive and functional status, depression, life satisfaction, social interactions, chronic health conditions, medications, and health services use. In each succeeding year, either a telephone or in-person follow-up survey was conducted. At the third in-person survey in 1992 to 1993, year 6 of the study, blood samples were obtained for a number of routine hematologic and blood chemistry determinations; a separate sample was obtained for a study of inflammatory and coagulation factors, including monoclonal immunoglobulin proteins. Information was also obtained on several measures of functional status, self-report of health conditions, life satisfaction and self-rated health (18,19,23,24).

The characteristics of the subjects who had blood drawn have been described in detail in a previous report (25). Of the 4,162 subjects initially interviewed from 1986 to 1987, there were 2,569 available for interview from 1992 to 1993 (1,265 had died and 328 were lost to follow-up or refused further follow-up). All 2,569 subjects were 70 years of age or older. Of these subjects, 269 were unable to consent to blood drawing because of cognitive impairment and 568 either refused or were unavailable for blood drawing. Thus, blood specimens were available in 1,732 subjects (25). This sample should be similar to other community-based samples drawn under conditions requiring informed consent.

Laboratory Methods

Blood was collected in EDTA-containing vacutainer tubes, placed on ice, and taken to the laboratory where it was centrifuged immediately to separate the plasma, which was promptly frozen at −70°C in 0.5 mL aliquots. Agarose gel electrophoresis of plasma samples was performed with the enhanced resolution Paragon SPEII (Beckman Immunosystem, Brea, California) using the routine procedure for the determination of monoclonal serum proteins (6,15). The presence of monoclonal or multiple monoclonal proteins was subsequently confirmed by standard immunofixation techniques using Beckman IFE kits. Densitometer tracings of the protein electrophoresis patterns were utilized to quantify the monoclonal immunoglobulin band as well as the non-monoclonal globulin fractions. Interleukin-6 (IL-6) levels were determined by enzyme-linked immunosorbent assay (ELISA) as previously described in detail (25).

Statistical Analysis

The prevalence of monoclonal gammopathies in different demographic, functional, disease, and blood variables were compared with chi-square analysis for discrete variables and by the nonparametric Wilcoxon rank-sum test, for continuous variables, which demonstrated significant skew. The association between health and functional status and the presence of monoclonal gammopathy was tested with the Spearman correlation. Multivariable estimates of the effect of these predictors on the presence of monoclonal gammopathies were estimated with a stepwise logistic regression using all the demographic, functional status, disease, and blood variables listed previously as candidate variables ($P \leq 0.05$ to enter and stay in the model).

RESULTS

Of the 1,732 subjects who had blood drawn, 106 (6.1%) had a monoclonal gammopathy. There was a greater than twofold difference in prevalence between blacks (8.4%) and whites (3.8%). There was a slightly greater prevalence in males and a trend toward greater prevalence with increasing age. When blacks and whites were analyzed separately, the same trends were noted. Urban/rural status and education were not associated with monoclonal gammopathy prevalence (Table 1).

Incomes (median $6,000) in those with or without monoclonal gammopathy were similar ($P = 0.99$). Because of the previous association of certain occupations and exposures with the occurrence of myeloma, we assessed whether employment in such occupations (eg, metal work, wood work, farming, radiation-related work) (26,27) differed among the blacks and whites with monoclonal gammopathy. No differences were found; 21% of whites and 27% of blacks with monoclonal gammopathy had had potential exposure to these occupations ($P = 0.5$).

There was no association between presence of monoclonal gammopathy and functional states, or instrumental activities of daily living (all $P > 0.2$). There was no

Table 1. Sample Characteristics and Prevalence of Monoclonal Gammopathies

Value	N with Monoclonal Gammopathy/ Total N	Prevalence of Monoclonal Gammopathy	*P*
Black race	77/916	8.4%	
Non-black race	29/816	3.6%	
			<0.001
Men	47/606	7.8%	
Women	59/1126	5.2%	
			0.04
Rural/urban status			
Rural	51/804	6.3%	
Urban	55/928	5.9%	
			0.72
Age (yrs)			
70–79	63/1160	5.4%	
80–89	38/517	7.4%	
90–99+	5/55	9.1%	
			0.07
Education (yrs)			
0–11	84/1276	6.6%	
12	6/157	4.0%	
13	13/290	13.0%	
Missing	3/9	33.0%	
			0.002

significant correlation with life satisfaction ($P = 0.84$), but those who rated their health as poor had a slightly higher prevalence of monoclonal gammopathy ($P = 0.04$). None of the health conditions surveyed, including cancer, cardiovascular disease, cerebrovascular disease, diabetes, hip fracture or other broken bones, or arthritis, showed any correlation with monoclonal gammopathy prevalence (all $P > 0.24$). This indicates that general health and disease status did not differ significantly between those with and without monoclonal gammopathy.

Since there was no direct clinical examination of subjects, there is no way to determine whether any of the subjects with monoclonal gammopathy had evidence of related active disease, such as myeloma. However, other laboratory studies, including complete blood count, other serum proteins, and measurement of IL-6, had been performed on these subjects. There were no differences in IL-6 levels, blood urea nitrogen, or serum calcium levels between those with or without monoclonal gammopathies (Table 2). Hemoglobin and albumin levels were slightly lower and serum creatine levels slightly higher in the monoclonal gammopathy group. In multivariate analysis (Table 3), however, only race, gender, and age remained as independent correlates of monoclonal gammopathy. There were no independent associations with these other markers of disease status.

Table 3. Multivariate Predictors of the Presence of Monoclonal Gammopathies

Variable	Odds Ratio	95% Confidence Interval	*P*
Age (per 10 years)	1.56	1.11, 2.20	0.011
Male	1.69	1.12, 2.56	0.012
Black	2.46	1.59, 3.82	0.0001

Determination of the characteristics of the monoclonal proteins revealed that the immunoglobulin class was predominantly IgG (65%); 5% were IgA, 10% were IgM, and 17% were biclonal or multiclonal. The kappa to lambda light chain ratio was 1.2. Monoclonal proteins were predominantly of low concentration, with 45% less than 0.5 g, 23% 0.5 to 1 g, 25% 1 to 2 g, and 7% >2 g (Table 4). There were no differences between blacks and whites in any of these characteristics.

Within the monoclonal gammopathy group, there was no correlation between IL-6 level and monoclonal protein level (Figure). There was no difference in IL-6 levels of black compared with white subjects with monoclonal gammopathies (blacks, median = 1.72 pg/mL; whites, median = 1.72 pg/mL; $P = 0.49$).

Table 2. Relationship of Monoclonal Gammopathies with Other Blood Variables*

Variable	Monoclonal gammopathy		
	Present (n = 1606)	Absent (n = 1626)	*P*†
Interleukin-6 (IL-6) (pg/mL)	1.78 (1.03, 3.14)	1.69 (0.96, 2.96)	0.63
Calcium (mg/dL)	8.9 (8.7, 9.1)	9.0 (8.7, 9.3)	0.06
Blood urea nitrogen (mg/dL)	18 (14, 25)	17 (14, 22)	0.13
Hemoglobin (g/dL)	12.9 (11.5, 13.8)	13.2 (12.3, 14.2)	0.006
Albumin (g/dL)	4.1 (3.8, 4.3)	4.2 (3.9, 4.4)	0.006
Creatinine (mg/dL)	1.4 (1.1, 1.7)	1.2 (1.1, 1.4)	0.0001

* Values are median (25th, 75th percentiles).
† By Wilcoxon rank-sum test.

Table 4. Monoclonal Protein Quantification by Race

Grams/dL	White N (%)	Black N (%)	Total N (%)
<0.5	17 (59)	31 (40)	48 (45)
0.5 to <1.0	4 (14)	20 (26)	24 (23)
1.0 to <2.0	6 (21)	21 (27)	27 (25)
2.0 to <3.0	2 (7)	4 (5)	6 (5)
≥3.0	0 (0)	1 (1)	1 (1)

DISCUSSION

Multiple myeloma is a malignant disease of plasma cells that predominantly affects the elderly. Previous studies have indicated that it is more common in blacks than whites, and least common in Asians (8,12–14). The reasons for this variation are unknown. Although socioeconomic and other environmental factors have been suggested (26–29), a genetic predisposition may also be involved (30). Multiple myeloma has a precursor condition (MGUS) somewhat analogous to the relationship between colon cancer and adenomatous polyps (31,32). The prevalence of MGUS is approximately 200 times greater than multiple myeloma (9). It has been demonstrated to have a consistent rate of conversion to multiple myeloma (33–35). Both processes occur predominantly in the elderly (1,9). The advanced age of many patients with idiopathic monoclonal gammopathies means that most of these individuals will die of other causes without ever developing multiple myeloma or other immunoproliferative disorders (35).

The evolution of multiple myeloma is thought to be a multistage carcinogenic process with the idiopathic monoclonal gammopathy occurring at an earlier stage (31). If the occurrence of monoclonal gammopathy differs by race in the same way as does multiple myeloma, this may indicate a racial/genetic influence at an early stage of the disease. In a previous study, we had found that the occurrence of monoclonal gammopathies in a Japanese population was lower than in Caucasians, similar to the difference in multiple myeloma reported for these racial groups (15). In that study, confounding factors such as differing chronic disease rates did not seem to be important, although we could not rule out possible socioeconomic and environmental causes.

In this study, we found that the prevalence of monoclonal gammopathy was more than twice as great in blacks as in whites, a difference similar to that reported for multiple myeloma incidence in these two racial groups (8). Moreover, possible confounders such as socioeconomic status, comorbidities, and environmental exposures through such factors as occupation, did not appear to influence this relationship, suggesting a true genetic difference in prevalence.

The importance of measuring the prevalence of monoclonal gammopathy in a community-based sample is emphasized by the work of Lithgart et al (5), who showed that in elderly subjects, monoclonal gammopathy prevalence was progressively higher in groups with increasing disease status. Prevalence was lowest in "optimally healthy" subjects, intermediate in apparently healthy retirement residents and outpatients, and highest in inpatients (5). The two previous studies that demonstrated a greater prevalence of monoclonal gammopathies in

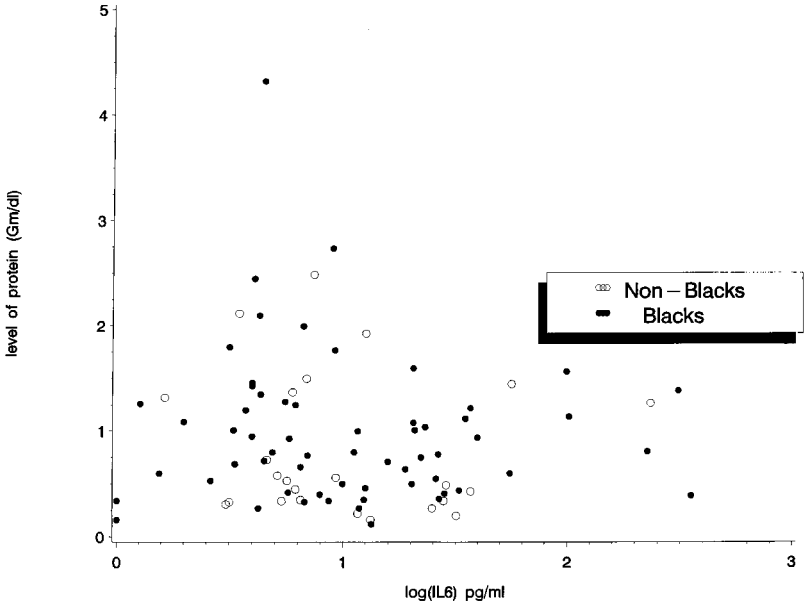

Figure. Correlation between level of monoclonal protein and IL-6 among patients with monoclonal gammopathy.

blacks were performed on male veteran patients who had had protein electrophoresis ordered for diagnostic purposes (16,17), a highly selected group. In one study, the prevalence of monoclonal gammopathy was 14% in blacks and 7.8% in whites (16). These rates are approximately twice those in our study, perhaps because the study may have included patients with immunoproliferative disorders. In addition, the investigators performed immunofixation electrophoresis on all subjects, including those with no evidence of monoclonal protein electrophoresis (16). In our study, monoclonal proteins were first detected by agarose gel electrophoresis, with immunofixation used to confirm the immunoglobulin characteristics and type. In another study, using comparable methodologies, the prevalences in subjects 70 years of age and older were comparable to ours (6.5% in blacks, 4.8% in Caucasians) (17).

The lack of association between socioeconomic and other demographic and health factors and the prevalence of monoclonal gammopathy in blacks and whites strongly suggest a genetic basis for the relationship. Although we cannot rule out other unknown environmental factors that may contribute, occupation and urban/rural differences were not associated with the variation in racial prevalence in our analyses. Others have attempted to study the possible genetic basis for the black/white differences in multiple myeloma. An association with HLA type has been demonstrated, but it is not fully explanatory. The excess prevalence of HLA CW2 in blacks is not great enough to explain the difference in prevalence of disease (30). An increased frequency of a gene deletion on chromosome 13 has also been described in blacks with multiple myeloma and with MGUS (36). Other possibilities include increased immune stimulation or response. However, previous studies have not supported this hypothesis (13,37).

In this study, we confirm that male gender and increasing age are independently associated with the prevalence of monoclonal gammopathies (36). It has been suggested that the effects of age are related to age-related immune dysregulation. Further evidence of such dysregulation is the increased frequency of biclonal proteins in the older age group (6,37).

The types and quantities of monoclonal proteins in this study are similar to those seen in previous reports (40). There were no striking differences between blacks and whites. Previous reports have indicated that elevated IL-6 levels are seen in patients with multiple myeloma, that levels are greater in myeloma than in monoclonal gammopathies, and that the elevated levels correlate with severity of disease in myeloma (41,42). Other studies have shown much less striking changes, even in severe myeloma (43). In our study, we found no difference in the levels of IL-6 between those subjects with and without monoclonal gammopathy, nor was there any correlation between IL-6 levels and the level of monoclonal protein in those with monoclonal gammopathy.

We have demonstrated, in a community-based population sample, that age-related monoclonal gammopathies are more prevalent in blacks than whites and confirm the association with increasing age and male gender. In conjunction with our previous data, this confirms a progressively increasing prevalence of monoclonal gammopathy comparing Asians, Caucasians, and blacks that is of a similar order and magnitude as that seen for the incidence of multiple myeloma. This suggests that the pivotal event determining these racial differences occurs early in the development of the disorder. In the absence of obvious socioeconomic and environmental explanations, it may lie in a genetic predisposition to a carcinogenesis-initiating event.

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