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High prevalence of polyclonal hypergamma-globulinemia in adult males in Ghana, Africa

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Abstract

Chronic antigenic stimulation is associated with hypergamma-globulinemia. Higher rates of hypergamma-globulinemia in tropical populations are maintained even with migration to temperate regions. We conducted a population-based screening study to assess the prevalence and risk factors for hypergamma-globulinemia in Ghana, Africa. 917 Ghanaian males (50–74 years) underwent in-person interviews and health examinations. Serum from all persons was analyzed by electrophoresis performed on agarose gel; serum with a discrete/localized band was subjected to immunofixation. 54 persons with monoclonal proteins were excluded and 17 samples were insufficient for analysis. Using logistic regression and Chi-square statistics we analyzed patterns of hypergamma-globulinemia. Among 846 study subjects, the median γ-globulin level was 1.86 g/dL. On the basis of a U.S. reference, 616 (73%) had hypergamma-globulinemia (>1.6 g/dL) and 178 (21%) had γ-globulin levels >2.17 gm/dl. On multivariate analyses, lower education status ($P = 0.0013$) and never smoking ($P = 0.038$) were associated with increased γ-globulin levels. Self-reported history of syphilis was associated with hypergamma-globulinemia. We conclude that three quarters of this population-based adult Ghanaian male sample had hypergamma-globulinemia with γ-globulin levels >1.6 g/dL. Future studies are needed to uncover genetic and environmental underpinnings of our finding, and to define the relationship between hypergamma-

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Author Contributions FB, AWH, JAK, RAK, SVR, and OL initiated the study. AWH provided samples and data (originally obtained in the Ghana Prostate Cancer Screening study). JAK and RAK interpreted all the serum assays. RMP did all the statistical modeling and ran all the statistical analyses. FB and OL drafted the manuscript. All the authors interpreted the results and read and approved the final manuscript.

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globulinemia, monoclonal gammopathy of undetermined significance (MGUS), and multiple myeloma.

Introduction

Humoral immunity is maintained by a complex series of events involving antigens, B-lymphocytes, T-cells, macrophages, and cytokines [1,2]. A well organized series of events results in B-cell stimulation, proliferation, and transformation into memory B-cell and immunoglobulin producing plasma cells. These highly specific immunoglobulins are involved in protecting the body against foreign tissue or pathogens, such as bacteria and their toxins, viruses, malignant cells, and foreign tissue. The level of immunoglobulin production is dependent on several factors. including antigenicity of the foreign tissue, immunogenicity, prior exposure, and an intact immune system [3].

Deficiency or low levels of γ-globulins are well known to be associated with clinical immune dysfunction, characterized by increased risk for infections, mostly notable in the respiratory tract [4]. Conversely, diffuse or polyclonal hypergamma-globulinemia has been found to occur more often among individuals affected by various types of immune-related and inflammatory conditions (such as autoimmune-, infectious-, and chronic-inflammatory disorders [5,6]). Interestingly, the quantitative level of γ-globulins in the blood has been reported to vary between racial/ethnic and socioeconomic groups, and across geographical regions, suggesting an interaction between host-related susceptibility genes and environmental factors [7-9]. In further support of germ-line genes playing a role in immune responses, previous studies have shown differences in γ-globulin levels among whites and blacks living in the same geographical region with similar exposure to infections [10,11]. Also, indigenous people from the tropics who have migrated to the temperate regions for several centuries have been found to still maintain high γ-globulin levels implicating a role for genetic differences in immune responses [12,13].

Previous investigations have found multiple myeloma, and its precursor monoclonal gammopathy of undetermined significance (MGUS) to be two- to three-fold more common among blacks than whites [14-16], supporting the theory of race-related susceptibility genes. At the same time, there is recent evidence to support that chronic immune stimulation causing polyclonal hypergamma-globulinemia, might serve as an immunological stimulus for progression to MGUS and hematological malignancy [17]. Given these observations, we were motivated to assess the prevalence and risk factors for polyclonal hypergamma-globulinemia in an urban community in Ghana, Africa.

Methods

Study subjects

Informed consent was obtained from all study subjects, and the study sample collection was approved by the Institutional Review Boards of the United States National Cancer Institute (NCI) and the University of Ghana. To enroll a population-based probability sample into the study, we used the 2000 Ghana Population and Housing Census data to construct a sampling frame of men aged 50–74 years in the Greater Accra region (approximately 3 million people). We estimated that about 7,500 households would need to be sampled to identify ~1,000 eligible men for the study. To achieve this, probability samples were selected in three stages: well-defined geographic boundaries in Accra were the primary sampling unit, with households in the enumeration areas as the secondary sampling unit, and males aged 50 to 74 years living in the household as the ultimate sampling unit. At the first stage of sampling, 300 enumeration areas were selected randomly with probability proportional to

size (the PPS method), the measure of size being the number of households in each enumeration area. At the second stage, a listing of households in each enumeration area was produced by the Ghana Census Bureau and 25 households were selected randomly from each enumeration area to produce a total of 7,500 households from the Greater Accra Region. The third stage involved door-to-door visits of the 7,500 selected households to enumerate all members of the household and identify eligible men for the study. The respondent for the survey was selected from the eligible adult male members (aged 50–74 years) of the household; where there was more than one eligible respondent, the one with the earliest month of birth was selected. Initially, we identified 971 eligible men from these households. Of these, three were too sick to be screened and nine refused to participate, yielding a 98.8% (959/971) response rate. We further excluded 42 men with a history of cancer leaving 917 men for further analysis.

Interview and collection of biological samples

Consenting participants were brought to the Korle-Bu Teaching Hospital for health examination and blood collection. Information on risk factors, including smoking, use of alcohol, body size, family history of cancer, and medical history as well as screening practices and utilization of the medical care system, were elicited from all study subjects through an in-person interview by trained interviewers using a structured questionnaire. A total of 20 ml of overnight fasting blood was collected from each participant. Collected blood was brought to the central laboratory within 2 hr of collection for processing and then stored at −70°C at the Korle-Bu Teaching Hospital. Subsequently, specimens were shipped on dry ice by express mail to the NCI repository in Frederick, Maryland, for long-term storage.

Laboratory tests and statistical analysis

All serum samples were processed and analyzed in an identical fashion and in the same laboratory at Mayo clinic. The samples were thawed and analyzed on average one and a half years (range: 1–2.5 years) after collection. Electrophoresis was performed on agarose gel (REP, Helena Laboratories). The agarose strip was inspected by a technician and by two of the authors (RAK and JAK). Any serum with a discrete band or thought to have a localized band was subjected to immunofixation (Hydrasys and Hydragel, Sebia). All samples with a monoclonal protein on immunofixation were excluded ($n = 54$), also 17 samples were lost or insufficient for analysis, leaving 846 samples for the final analysis including quantification of γ-globulin levels.

Hypergamma-globulinemia was defined as γ-globulin levels above 1.6 g/dL, based on the reference range used in clinical laboratories. We analyzed associations of select characteristics and protein levels based on several models, which accommodated the multistage sampling design, using the SUDAAN software. First, we categorized protein levels into quartiles and fit proportional odds models (Proc Multilog, SUDAAN). We then also fit linear regression models to the log-transformed protein levels. As the log-transformed levels were not normally distributed, we applied restricted linear models to those observations falling between the lowest fifth and highest 95th percentile, to lessen the sensitivity to outliers (Proc Regress, SUDAAN). Univariate models were adjusted for age in quintiles, fitted with a trend. All *P* values are two-sided.

Results

Table I shows selected characteristics of the 846 study subjects. The median age of the study population was 60 years (range 50–74). The median γ-globulin level was 1.86 g/dL (range 0.81–5.59). Seventy-three percent of the samples had γ-globulin level greater than 1.6 g/dL

(Mayo Clinic laboratory reference range 0.6–1.6 g/dL), and thus meeting the definition of hypergamma-globulinemia. Twenty-one percent had γ-globulin levels above 2.17 g/dL. Forty-four percent had history of tobacco use, while 32% had history of some alcohol use. One third of the study subjects had a high school or higher education, with only 18% having primary school or less education. Malaria (83.6%), yellow fever (10.5%), measles (27.5%), gonorrhea (42.6%), and genital herpes (7.1%) were the most frequently reported prior infection.

First, we assessed γ-globulin levels by quartiles (<1.6 g/dL; 1.6-1.87 g/dL; 1.88–2.17 g/dL; >2.17 g/dL) in relation to demographics, socioeconomics, and history of selected prior infections. Using this unadjusted descriptive approach, we found increasing age ($P = 0.008$) and lower education status ($P < 0.0001$) to be associated with higher polyclonal γ-globulin levels. Also, a medical history of genital warts ($P = 0.03$) or genital herpes ($P = 0.04$) was associated with higher polyclonal γ-globulin levels. Neither smoking nor alcohol was statistically associated with polyclonal γ-globulin levels.

Second, we fit regression models accommodating multistage sampling design to analyze the association between γ-globulin levels (as a continuous variable) and demographics, socioeconomics, and history of selected prior infections. On univariate analyses, older age ($P = 0.0002$) and lower educational status ($P = 0.003$) were significantly associated with higher polyclonal γ-globulin levels, and a medical history of syphilis ($P = 0.0049$) or hepatitis B/C ($P = 0.0095$) were significant. Multivariate analyses revealed older age ($P = 0.019$), never smoking ($P = 0.038$), and lower educational status to be significant ($P = 0.0013$). Significance of educational status remained upon subanalysis by educational status (postsecondary, secondary, primary, or none; data not shown). Additionally, a personal medical history of syphilis ($P = 0.014$) was an independent factor associated with higher γ-globulin levels. Although hepatitis B/C infection appeared significant in the multivariate linear regression model, significance did not remain in the proportional-odds model. As results were otherwise similar, we report findings for the linear model only in Table II.

Discussion

We found that three quarters of almost 1000 adult males above the age of 50 years in Accra, Ghana, had polyclonal hypergamma-globulinemia based on current reference range used in most American laboratories. Older age, never smoking, and lower educational status, as well as a personal history of syphilis, were associated with higher γ-globulin levels. Our findings support the hypothesis that gene-environment interactions might play an important role in immune responses causing polyclonal hypergamma-globulinemia, and, which in turn, might be a pathway to MGUS and subsequent hematological malignancies [17].

Our finding of a very high prevalence of polyclonal hypergamma-globulinemia in adult Ghanaian males is in accord with prior smaller studies showing racial/ethnic differences in γ-globulin levels [10,12,18]. The possibility of this being due to, at least in part, some genetic predisposition is supported by studies that have shown significant differences in γ-globulin levels between racial/ethnic groups that have lived in the same geographic region and thus having had similar environmental exposures for several years [8,19,20]. In a study by Curtain et al. in Australia the γ-globulin level in Europeans living in the same region were lower than the natives. The large number of healthy subjects in our study with hypergamma-globulinemia also supports a common denominator, such as genetic influence.

Interestingly, the racial disparity in polyclonal hypergamma-globulinemia parallels the disparity seen in other plasma cell proliferative disorders, such as MGUS and multiple myeloma. We have reported that the age adjusted incidence of monoclonal gammopathy of

undetermined significance (MGUS) a precursor of multiple myeloma and multiple myeloma itself is two-fold higher in blacks than in Caucasians [14]. We recently also found and reported a similar two-fold increase in incidence of MGUS in Ghanaians males [21]. Although a relationship between polyclonal hypergamma-globulinemia and the development of monoclonal gammopathy has not been fully established, the higher incidence of both conditions in the same population group suggests a possible relationship. Although it remains to be proven in future studies, based on our clinical experience, we do believe that polyclonal hypergamma-globulinemia is a precursor to certain B-cell lymphoproliferative and plasma cell proliferative disorders. These findings are thus supportive of the theory that differences in genetic susceptibility may account for this higher incidence of plasma cell disorders.

When we assessed associations between selected factors and γ-globulin concentrations, we found a personal history of syphilis to be associated with higher γ-globulin levels. We also found older age, never smoking, and lower educational status to be associated with higher γ-globulin levels. Syphilis is often a chronic infection if untreated and has the potential for multiple reinfections following treatment; hence, syphilis infection may cause repeated antigenic stimulation of toll-like receptors [22]. This observation is consistent with prior reports that have recognized chronic immune stimulation to be important in the development of B-cell disorders, such as polyclonal gammopathy, MGUS, lymphomas, and cryoglobulinemia [23]. Certainly it is not clear whether these infections are the initial trigger for the development of these B-cell disorders or act as a second hit in people already prone to the development of these conditions as a result of a genetic predisposition [14]. In the case of smoking this is similar to what was reported in a study by Mili et al. 1991 and others [10,18,20] which showed that smokers had lower γ-globulin levels with return to normal levels on cessation of smoking. In the case of educational status, we believe that this is tied to socioeconomic status and lower utilization of health services. The decreasing γ-globulin levels in this region over the past 2 to 3 decades with improvement in health services and health care delivery confirms the role of environmental factors [24].

In addition to the above discussion about pathogenetic mechanisms and etiologic risk factors for plasma cell disorders, our study certainly brings into question what the reference cut-off for hypergamma-globulinemia should be in this population. Typically, normal reference ranges are defined based on young healthy adults. Our finding that the vast majority of 846 Ghanaian adult males 50–74 years of age, based on the western cut-off, were defined as having hypergamma-globulinemia suggests the 1.6 g/dL cut-off might not be appropriate for this population. However, at the same time, caution must be taken in making a change in the reference range, especially if hypergamma-globulinemia in these communities is a disease state or a precursor to other diseases that may require therapeutic intervention. A larger study looking at all demographic and specific serum screening for prior infection will help define a meaningful reference range in this population, thus making this test a useful trigger for further evaluation.

On the basis of restricted number of smaller studies, it has been suggested that the striking two- to three-fold excess of multiple myeloma and MGUS among blacks [14-16] may be due to differences in socio-economic status (i.e., environmental and behavioral factors); however, the literature is controversial. Indeed, some studies have reported elevated risk of multiple myeloma associated with lower socio-economic status (based on education and income status) among both African-Americans and whites [25,26], some have found elevated risk of multiple myeloma mortality with higher social class [27,28], and other studies have found no association between socio-economic status and multiple myeloma [29]. Furthermore, there is emerging evidence from large population-based studies that obesity is associated with an up to two-fold elevated risk of developing multiple myeloma

[30,31]. Previous studies have found elevated levels of proinflammatory cytokine interleukin (IL)-6 in obese persons [32] and it has been suggested that as much as 30% of total body IL-6 may be secreted by adipocytes in obese individuals [32]. Because blacks have higher rates of obesity in the U.S. (compared with whites), it has been proposed that the excess of MGUS and multiple myeloma in blacks may be due to differences in body mass index (BMI). Very recently, we conducted a large MGUS screening study based on the population-based U.S. Southern Community Cohort Study cohort [33]. We screened 1,000 African-Americans and 996 Caucasians for MGUS, and we had access to extensive questionnaire data with which to evaluate the effect of several potential confounders of the race-MGUS association. In that study, the doubling of risk for African-Americans was virtually unchanged when we included obesity, education status, and income status in the same multivariate model [34]. These findings are supportive of this study in that they suggest that the racial difference with regard to MGUS and multiple myeloma is not an artifact of differences in socioeconomic status, and strengthen the hypothesis that susceptibility genes play a role in the observed race-related differences with regard to immune reactivity [15,17,21,35,36].

The major strength of this large population-based study include its inclusion of probability samples from the population, high response rate, high quality in person interview, and rigorous quality control procedures, as well as serum protein analysis performed at the Mayo clinic. Limitations include the unavailability of a fully detailed medical history, which may have led to under estimation of comorbidity (such as infections other than those included in the questionnaire) and lack of data on medication use. Also, as described in the Methods section, medical history data were obtained through an in-person interview by trained interviewers using a structured questionnaire; however, we did not have data from medical records or laboratory tests to confirm these self-reported medical conditions. Another limitation is the lack of information on γ-globulin levels in women and younger population. Additional investigations are needed to confirm our findings and also expand the study to include women as well as persons younger than 50 years of age.

In summary, based on a large population-based sample of Ghanaian adult males, we found three quarters of the study subjects to have high γ-globulin levels >1.6 g/dL supporting a role for germ-line genes playing a role in humoral immune responses reflected in γ-globulin secretion. High γ-globulin levels were found to be associated with age, never smoking, lower education status and a personal history of syphilis infection. Our results support the theory that genetic determinants of immune reactivity possibly accompanied by ill-defined environmental factors underlie the observed susceptibility to hypergamma-globulinemia in blacks. Future studies are needed to confirm and expand our findings.

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TABLE I
Selected Characteristics of Study Population (*N* = 846)

Variables ~ Q	
Median age (range) years	60 (50–74)
Gamma-globulin concentration (g/dL), median (range)	1.86 (0.81–5.59)
Smoking, n (n/N; %)	
Never	458 (56.5)
Ever	244 (30.1)
Current	108 (l3.3)
Alcohol intake, n (n/N; %)	
Never	368 (68.3)
Ever	171 (31.7)
Education Status, n (n/N; %)	
None/primary	144 (18.0)
Middle/junior secondary	380 (47.5)
Secondary/senior secondary/higher	278 (34.6)
Self-reported history of selected infections, n (n/N; %)	
Malaria	693 (83.6)
Tuberculosis	12(1.5)
Cholera	24 (2.9)
Yellow fever	85 (10.5)
Measles	207 (27.5)
Gonorrhea	358 (42.6)
Hepatitis B/C	10 (1.3)
Genital herpes	59 (7.1)
Genital warts	5 (0.6)
Syphilis	27 (3.4)

N = total number of individuals with available information

TABLE II

Associations Between Polyclonal Protein Level[a], Older Age, Smoking, Education Status, and Self-Reported History of Selected Infections

		Univariate[b]			Multivariate[c]		
Variable	**Obs. (n)**	**Δ γ-globulin (%)**	**95% CI (lower, upper)**	***P*-value**	**Δ γ-globulin (%)**	**95% CI (lower, upper)**	***P*-value**
Older age	846	1	(1,2)	0.0002	1	0,1	0.019
Smoking Status	810	−1	−3,0	0.15	−2	−4,0	0.038
Alcohol	480	−1	−3,2	0.57	0	−3,3	0.97
Lower Education Status	722	4	1,7	0.0030	5	2,7	0.0013
Medical history[d]							
Malaria	745	−2	−6,2	0.33	−5	−12,1	0.12
Tuberculosis	743	−4	−9,2	0.17	−4	−10,2	0.19
Cholera	738	1	−6,9	0.73	2	−6,10	0.66
Yellow Fever	730	0	−3,3	0.95	0	−4,3	0.78
Measles	678	−1	−4,1	0.26	−1	−4,1	0.23
Syphilis	718	7	2,12	0.0049	7	2,13	0.014
Gonorrhea	758	0	−2,2	0.93	0	−2,1	0.63
Hepatitis B/C	678	−6	−11,−2	0.0095	−5	−10,−1	0.024[e]
Genital Herpes	741	0	−5,4	0.86	1	−4,5	0.80
Genital Warts	752	−5	−9,0	0.052	−4	−11,3	0.23

Δ γ-globulin is based on the standardized regression coefficient of each variable against the gamma-globulin concentration. It is the percent change in gamma-globulin from a change of one standard deviation of the listed variable.

Regression coefficients determined using reported history of never smoking, not drinking alcohol regularly, secondary or higher education, and no reported history of infection as reference values.

Obs = observations; CI = confidence interval

[a] Protein level as a continuous variable.

[b] All estimates adjusted for age.

[c] All estimates simultaneously adjusted for all other variables in the table, including participants with missing responses for personal history of one or more infectious diseases.

[d] Self-reported medical history.

[e] These p-values became nonsignificant in the proportional-odds model. All other values were of similar magnitude in the proportional-odds and linear regression models.