Predictors of shingles reports at diagnosis of common variable immunodeficiency and selective immunoglobulin G subclass deficiency in 212 Alabama adults

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Abstract

We sought to determine predictors of shingles reports in adults with common variable immunodeficiency or immunoglobulin (Ig) G subclass deficiency (CVID/IgGSD). We tabulated observations at diagnosis of CVID/IgGSD in 212 white adult index patients (165 women, 47 men) who responded to a question about having had shingles. None had been vaccinated for herpes zoster. We analyzed age, sex, and shingles reports; blood levels of CD19+, CD4+, CD8+, and CD56+ mononuclear cells; serum levels of IgG subclasses, IgA, and IgM; and positivity for human leukocyte antigen (HLA)-A and -B haplotypes. Cell counts and immunoglobulin levels were normalized with loge (ln) transformation for analyses. None had been vaccinated for herpes zoster. Responded to a question about having had shingles was almost five-fold greater in CVID/IgGSD diagnosis, the prevalence of recurrent infections, and positivity for HLA-A*01, B*08 were associated with shingles reports [P=0.0151; odds ratio (OR) 1.05, 95% confidence interval 1.01, 1.08]. HLA-A*01, B*08 positivity was also positively associated with shingles reports [P=0.0480; odds ratio 2.61 (1.00, 6.81)]. We performed a retrospective evaluation to characterize shingles in 212 white adults with CVID/IgGSD and to determine the relationship of age at diagnosis of CVID/IgGSD, sex, blood mononuclear cell subset levels, serum immunoglobulin isotype levels, and HLA-A and -B haplotypes with reports of shingles. Our observations are discussed in the context of previous reports of factors that appear to provide defense against (or increase risk of) herpes zoster.

Materials and Methods

Patient selection

The performance of this work was approved by the Institutional Review Board of Brookwood Medical Center. All patients reported herein were referred to a hematology and medical oncology practice for further evaluation and management because they had increased frequency or severity of infections uncontrolled by antibiotic therapy and evidence of hypogammaglobulinemia. We defined probable CVID in accordance with the criteria of the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiency. In adults, these criteria include men or women with a decrease of serum IgG and IgA at least 2 standard deviations (SD) below the mean for age; absent isohemagglutinins or poor response to vaccines; and exclusion of other defined causes of hypogammaglobulinemia. There is no generally accepted definition of IgGSD. In one reference, IgGSD was defined as deficiency of one or more IgG subclasses (IgG1-3) at least 2 SD below the mean for age in the presence of normal total serum IgG levels, with or without IgA deficiency. We defined that patients with subnormal total IgG levels but whose IgA levels were normal also had IgGSD. Each patient diagnosed to have IgGSD in the present study was also demonstrated to have impaired response to polysaccharide antigens of Streptococcus pneumoniae and had no other defined cause of hypogammaglobulinemia.

We performed a computerized and manual

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search of charts of all white adults (≥18 years of age) in our practice who were referred as outpatients in the interval 1998-2008 because they had recurrent or severe infections, typically of the upper and lower respiratory tract, and who were diagnosed to have CVID/IgGSD.14,15 We designated the first persons in respective families diagnosed to have CVID/IgGSD as index patients. All index patients resided in central Alabama.

For final analyses, we included the 212 index patients whose charts: i) documented laboratory testing to establish their diagnosis of CVID/IgGSD, including flow cytometric analysis of blood mononuclear cells and HLA-A and -B haplotyping; ii) included responses to a question about history of shingles (or herpes zoster) diagnosed by a physician; and iii) contained a physician’s recommendation that they be treated with either intravenous or subcutaneous IgG because they had serious or recurrent infections. Most index patients were diagnosed to have CVID before zoster vaccine was licensed in the US in May 2006.1 No index patient diagnosed to have CVID/IgGSD herein reported that he/she had received zoster vaccine.

**Patient exclusions**

We excluded subjects with isolated deficiencies of IgA or IgM, normal immunoglobulin levels with deficiency of selective antibody specificity for *Streptococcus pneumoniae* polysaccharide antigen(s), or hypogammaglobulinemia attributed to B-cell neoplasms, organ transplantation, immunosuppressive therapy, or increased immunoglobulin loss. We excluded patients known to have infection with human immunodeficiency virus (HIV). We excluded shingles reports of three index patients (1.4%) because subsequent clinical and laboratory evaluations indicated that their recurrent skin eruptions were due to herpes simplex (eczema herpeticum).

We excluded persons of African American descent because: i) certain HLA types and haplotypes differ significantly among Caucasians and African Americans in central Alabama;16,18 ii) in adults, mean serum concentrations of immunoglobulins are often greater in persons of sub-Saharan African descent than in whites;19,20 and iii) persons of sub-Saharan African descent occur infrequently in series of CVID or IgGSD patients,21 and such patients are also uncommon in our experience.

**Laboratory methods**

Testing was performed at diagnosis of CVID/IgGSD before IgG replacement therapy was initiated. No patient had herpes zoster at diagnosis. Serum concentrations of total IgG, IgG subclasses, IgA, and IgM were measured using standard automated methods. Reference ranges for serum immunoglobulin concentrations are: total IgG 700-1600 mg/dL; IgG 41-129 mg/dL; IgG1 1-291 mg/dL; total IgA 70-400 mg/dL, and IgM 40-230 mg/dL. The lower and upper reference limits represent 2 SD below and above the corresponding mean value.3 Immunoglobulin deficiency was defined as a serum concentration was less than the corresponding lower reference limit; subtotal levels were confirmed in each patient. Reference ranges for blood levels of mononuclear cell subsets measured using flow cytometry are: CD19+ 12-645 cells/μL; CD3+ 622-2,402 cells/μL, CD4+ 359-1,519 cells/μL; CD8+ 109-897 cells/μL, and CD56+ 24-406 cells/μL.

HLA-A and -B alleles were detected using low-resolution DNA-based typing (polymerase chain reaction/sequence-specific oligonucleotide probe) in index cases.3 HLA typing of family members of some index cases was performed to permit assignment of chromosome 6p haplotypes. In each index patient in whom a single A or B allele was detected by DNA-based typing, we verified the allele(s) and set phase to ascertain haplotypes of the index patient using HLA analyses of appropriate family members. Haplotypes were defined only by A and B alleles.

**Statistical considerations**

Analyses were performed with Excel 2000® (Microsoft Corp., Redmond, WA) and GB-Stat® (v. 10.0, 2003, Dynamic Microsystems, Inc., Silver Spring, MD). Log (ln) transformation normalized the blood mononuclear cell subset counts and serum immunoglobulin levels. Serum levels of IgG below the detection threshold of 1 mg/dL were imputed as 0.5 mg/dL to permit ln transformation and inclusion of the data in all analyses.

We compiled four common HLA-A and -B haplotypes in the present cases that are associated with increased risk of CVID/IgGSD in central Alabama whites: A*01, B*08; A*03, B*07; A*02, B*44; and A*29, B*44.5,7 Preliminary univariable and regression analyses revealed that positivity for A*01, B*08 was the only potential HLA haplotype predictor of shingles reports. We did not include CD8+ mononuclear cell counts, CD4+/CD8+ ratios, or total serum IgG levels in regression analyses because these values are derivatives of or are less specific than CD4+ and CD8+ cell counts or IgG subclass levels alone. In a final thirteen-factor logistic regression model, we used reports of having (or not having) shingles as the dependent variable. The independent variables included: i) age at diagnosis; ii) sex; iii) ln-transformed blood levels of CD19*, CD4+, CD8+, and CD56+ mononuclear cells; iv) ln-transformed serum levels of IgG, IgG1, IgG2, IgG3, IgA, and IgM; and v) positivity for A*01, B*08.

Descriptive data are displayed as enumerations, percentages, mean±1 SD, or mean [95% confidence intervals (CI)]. Mean values were compared using a student t-test (two-tail). Frequency values were compared using chi-square analysis or Fisher exact test (one-tail), as appropriate. Correlations were expressed as Pearson correlation coefficient. A value of P<0.05 was defined as significant.

**Results**

**General characteristics of 212 index patients**

The mean age of all 212 patients was 48±13 years. Eleven patients (5.5%) had CVID. Two hundred and one patients (94.5%) had IgGSD; 75 of them (37.3%) had subnormal total IgG levels but their IgA levels were within the reference limits. The mean total IgG levels in patients with CVID was lower than that of patients with IgGSD (521 mg/dL [449, 604] vs. 777 mg/dL [748, 805], respectively; P=0.0001). Women comprised 77.8% of this cohort of 212 patients. Eight of 11 patients with CVID (72.7%) were women and 169 of 201 patients with IgGSD (84.1%) were women (P=0.2654).

**Comparisons of index patients with and without shingles reports**

Thirty-one patients (14.6%) reported previous episodes of shingles (Table 1). The proportions of patients with CVID and IgGSD who reported shingles did not differ significantly (0% vs. 15.4%, respectively; P=0.1678). The mean age of patients with shingles reports was greater than that of patients without shingles reports. Mean levels of blood mononuclear cell subsets and serum levels of immunoglobulin isotypes in patients with or without shingles reports did not differ significantly. The proportion of patients who were positive for HLA-A*03, B*08 was greater in those with shingles reports (Table 1).

**Shingles reports and age**

We analyzed shingles reports in patients grouped by age at CVID/IgGSD diagnosis (Figure 1). The overall prevalence in patients aged 18-49 years was 7.1% and that of patients 50-80 years was 23.2% (P=0.0009). There was a positive correlation of age and shingles reports (correlation coefficient 0.1927; P=0.0049).

**Characteristics of shingles reports in 31 index patients**

All 31 patients with shingles reports had IgGSD. The mean age of patients at the time of initial shingles episodes was 33±16 years (range 10-54 years) in the 11 subjects for whom this information was documented.
Charts of 24 patients (77.4%) documented dermatome patterns of skin eruptions, including five (13.1%) who reported trigeminal zoster. Ten patients (32.3%) reported recurrent shingles (2-4 episodes each). Two patients (6.5%) reported cutaneous dissemination of their eruption. Post-herpetic neuralgia was documented in a 38 year-old woman who developed trigeminal neuralgia after having had shingles on her face.

Predictors of shingles reports in a logistic regression model

In a 13-factor logistic regression model, age was a positive predictor of shingles reports [P=0.0151; odds ratio (1.05 (1.01, 1.08)]. HLA-A*01, B*08 positivity was also a positive predictor of shingles reports [P=0.0480; odds ratio 2.61 (1.00, 6.81)]. Odds ratios for all independent factors in the model are displayed in Figure 2. This model explained 22.3% of the variance in prediction of shingles reports.

Other evaluations based on age and HLA-A*01, B*08 positivity

The mean blood CD8+ mononuclear cell level of patients aged 18-49 years was higher than that of patients aged 50-80 years [438 cells/µL (402, 482) vs 367 cells/µL (326, 415), respectively; P=0.0077]. There was a negative correlation of age with blood CD8+ cell levels (correlation coefficient -0.2309; P=0.007). Comparisons of mean blood levels of CD19+, CD4+, and CD56+ mononuclear cells and of IgG subclass, IgA, and IgM levels revealed no significant differences between patients aged 18-49 years and those aged 50-80 years.

In persons with and without HLA-A*01, B*08, we compared mean values of age at diagnosis, blood levels of CD19+, CD3+, CD4+, CD8+, and CD56+ mononuclear cells, and serum levels of immunoglobulin isotypes. Index patients with A*01, B*08 had a lower mean IgG level than patients without this haplotype [189 mg/dL (52, 682) vs 244 mg/dL (83, 717); P=0.0203]. Other comparisons revealed no significant differences.

Occurrence of shingles after diagnosis of common variable immunodeficiency/immunoglobulin G subclass deficiency

We reviewed charts of the present 212 patients to determine the prevalence of shingles after diagnosis of CVID/IgGSD in a mean follow-up interval of 7.4±2.3 years during which the patients received monthly IgG replacement therapy. Eleven patients had shingles after diagnosis of immunodeficiency; each had IgGSD. The prevalence of shingles diagnosis in patients who previously reported having shingles was 16.1% (G31). The prevalence of shing-
gles diagnosis in patients who did not previously report having shingles was 3.3% (6/181). These proportions differed significantly (P=0.0119). The mean length of follow-up of the groups was similar (7.6±2.2 years and 7.4±2.8 years, respectively; P=0.8556). Five of six patients who reported having recurrent shingles before diagnosis of CVID/IgGSD had one or more additional episodes of shingles after they began receiving IgG replacement therapy.

Discussion

In the present study of CVID/IgGSD index patients, the mean age of patients with shingles reports was greater than that of patients who reported no shingles. We observed a greater prevalence of shingles reports in patients aged ≥50 years at diagnosis of CVID/IgGSD than in younger index patients, consistent with previous studies of subjects not stated to have CVID/IgGSD. Further, age was a significant independent predictor of shingles reports in the present regression analyses, although elevation of the odds ratio for shingles reports associated with age was minimal. Age is the most important risk factor for development of zoster in persons not specified to have CVID/IgGSD. In large studies of US cohorts, shingles risk increases significantly with age. In more than 4 million US health plan enrollees, shingles had occurred in 13.6% of persons aged 40-49 years and in 16.0% of persons aged 50-59 years. We observed that the overall prevalence of shingles reports in the present cohort was 14.6% at mean age of diagnosis of CVID/IgGSD of 48±13 years. Taken together, these observations suggest that the age-related risk of shingles in CVID/IgGSD patients is similar to that in non-CVID/IgGSD cohorts.

In a probability sample of community-dwelling persons >64 years old in North Carolina, Schmader et al. reported that interviewers administered a comprehensive health survey to 3206 participants that included questions about lifetime occurrence of shingles. After controlling for age, cancer, and demographic factors, blacks were one-fourth as likely as whites (adjusted odds ratio 0.25, 95% confidence interval 0.18-0.35; P=0.0001) to have experienced zoster. Thus, blacks had a significantly lower risk of developing herpes zoster than whites. In the present study, all patients were white. The percentage of the present white patients who reported having had zoster did not differ significantly from that in the study by Schmader et al. (14.3% vs 16.1%, respectively; P=0.5621). Zoster risk was greater in women than men in some reports. The prevalence of shingles reports we observed in women did not differ significantly from that in men, and sex was not a significant independent predictor of shingles reports, consistent with other studies. Recurrent herpes zoster and cutaneous dissemination were relatively common in the present index patients, consistent with characteristics of zoster in persons with immunocompromise due to conditions other than CVID/IgGSD.

Cases of recurrent shingles were identified by Yawn et al. in 669 persons 22 years of age or older in Minnesota who had a medically documented initial episode of shingles. Ninety-five of the 1669 (5.7%) had one or more recurrences of shingles during a mean follow-up interval of 7.3 years. Participants in this Minnesota cohort identified as having immunocompromise had a 2.35 hazard ratio for recurrent shingles. In the present study, ten patients (32.3%) reported recurrent shingles at diagnosis of CVID or IgGSD during a mean follow-up interval of 7.4 years. The observations in the present study and those of Yawn et al. support the conclusion that the prevalence of recurrent shingles is relatively high in persons whose immunity is decreased.

In the present study, there was a preponderance of women in both CVID and IgGSD subgroups, consistent with our previous report. The proportions of men and women in CVID cohorts typically do not differ significantly. In another report, there was a predominance of women among adults with IgG3 deficiency. The proportion of patients with CVID who also have or eventually develop autoimmune disorders is relatively high. The prevalence of autoimmune disorders is widely acknowledged to be greater in women than men. Our informal experience suggests that such patients are preferentially referred to our practice and thus could explain the predominance of women in the present cohort. Regardless, sex was not a significant predictor of risk for shingles reports in this study.

Cell-mediated immunity is important in the development of zoster and its manifestations. Helper/inducer phenotype (CD4+ or Leu3a+) proliferate in response to VZV, although proliferation testing is not a sensitive predictor of cellular immune compromise or risk of opportunistic infection. Helper/inducer T-lymphocytes are prominent in skin biopsy specimens from active herpes zoster lesions. Some functional properties of CD4+ cells are enhanced after exposure to VZV in vitro. In the present study, the levels of CD4+ blood mononuclear cells were not associated with shingles reports in univariable and regression analyses. It is unknown if numerical, proliferation, or functional deficits of CD4+ cells existed in the present shingles patients before they developed herpetic zoster. In previous studies of patients with CVID, circulating CD4+ cells responsive to immunization were decreased. Others had increased numbers of CD4+ cells, but the rate of apoptosis of these cells was also increased.

The numbers and cytotoxic activity of natural killer cells (CD16+, Leu17+, or CD56+) are depressed in the acute phase of herpetic zoster,
increase significantly in early convalescence, and return to normal in the late recovery phase.5,33 Some persons with severe deficiencies of natural killer cells have had severe VZV infections.5,6 In the present study, no patient had active or recent zoster. Mean numbers of CD56+ blood mononuclear cells did not differ significantly in patients with and without shingles reports, and blood levels of CD56+ cells were not significantly associated with shingles reports in logistic regression analyses.

Some cell-mediated immune responses to VZV decline with age.32,33 We observed a significant negative association of age with blood levels of CD8+ mononuclear cells, but neither blood levels of CD8+ cells mononuclear nor those of CD19+, CD4+, or CD56+ cells were significantly associated with shingles reports in logistic regression analyses.

Primary infection with VZV is associated with early production of IgM and IgG antibodies.47 The principal anti-VZV virus isotypes in plasma from healthy donors and from convalescents after primary and reactivated disease are in IgG, and IgG subclasses.48 IgG antibodies were present in zoster convalescents and healthy donors but were rarely detected in varicella convalescents. Anti-VZV IgG antibodies were found only in a few cases.48 In the present index patients with and without shingles reports, mean serum levels of respective immunoglobulin isotype levels did not differ significantly and were not significant independent predictors of shingles reports. We did observe that positivity for HLA-A*01, B*08 was greater in patients with shingles reports, and that the mean level of IgG was lower in index patients with HLA-A*01, B*08. IgG levels are also lower in healthy A*01, B*08 carriers.49 Taken together, these observations suggest that the positive association of HLA-A*01, B*08 and shingles reports we observed is not due to lower IgG levels. Measurement of anti-VZV antibodies in CVID/IgGSD index patients was beyond the scope of the present study.

HLA-A*01, B*08 is part of a common multigene haplotype on chromosome 6p. In Europeans, the haplotype typically includes HLA-DR3 and -DQ2. This haplotype is associated with increased risk of CVID and IgA deficiency and of systemic lupus erythematosus, myasthenia gravis, and other autoimmune disorders.50 We previously demonstrated that the prevalence of HLA-A*01, B*08 in Alabama whites with CVID/IgGSD was significantly greater than in white control subjects.51 HLA-A*01, B*08 is also associated with altered immunologic reactions to viral hepatitis and with an increased rate of progression of human immunodeficiency virus infection.51,52 The present results suggest that one or more factors in the HLA-A*01, B*08 haplotype increase the risk of shingles in patients with IgGSD. Nonetheless, the identities and roles of precise factors in the HLA-A*01, B*08 haplotype that affect manifestations of associated autoimmune and infectious diseases remain largely undefined.

Validating the accuracy of self-reports of shingles was not possible in this study. In a study of 4162 elderly persons, however, there were few false-positive and false-negative self-reports of zoster when compared to physician diagnosis.54 All charts of the present 31 patients with shingles reports documented distinctive characteristics of herpes zoster diagnosed by a physician. Thus, it is unlikely that primary varicella infection/chicken pox was erroneously diagnosed to be herpes zoster in these cases. Taken together, these observations suggest that the shingles reports we analyzed are accurate. We cannot exclude the possibility that some patients with herpes zoster with mild manifestations did not report their condition, or that such cases were not correctly diagnosed by physicians. It is plausible but unproven that rates of shingles reports would have been higher had our case series included a greater proportion of patients with more severe immunologic abnormalities. Therefore, our prevalence estimates of shingles reports may be conservative.

**Conclusions**

We conclude that age is positively associated with shingles reports in white adults at CVID/IgGSD diagnosis. The age-related risk of shingles in CVID/IgGSD patients is similar to that in previous studies of non-CVID/IgGSD cohorts. Recurrent herpetic zoster and cutaneous dissemination were relatively common in the present index patients, consistent with characteristics of zoster in persons with immunocompromise due to conditions other than CVID/IgGSD. We observed a positive association and increased odds ratio of HLA-A*01, B*08 positivity with shingles reports, although the basis of this association remains unknown.

**References**


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