Fibromyalgia in 300 adult index patients with primary immunodeficiency

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ABSTRACT

Objective. *We sought to determine the prevalence and clinical and laboratory associations of fibromyalgia in adults with primary immunodeficiency (immunoglobulin (Ig) G subclass deficiency (IgGSD) and common variable immunodeficiency (CVID).*

Methods. *We performed a retrospective analysis of these observations in 300 non-Hispanic white adult index patients with recurrent/severe respiratory tract infections and IgGSD or CVID: age; sex; IgGSD; fibromyalgia; chronic fatigue; autoimmune conditions (ACs); interstitial cystitis (IC); diabetes; body mass index; serum Ig isotypes; blood lymphocytes and subsets; and human leukocyte antigen (HLA)-A and -B types and haplotypes. We performed univariate comparisons, logistic multivariable regressions, and an analysis of covariance.*

Results. *Mean age was 49 ± 12 (standard deviation) years. There were 246 women (82.0%). IgGSD was diagnosed in 276 patients (92.0%). Fifty-six patients had fibromyalgia (18.7%; female:male 13:1). Other characteristics included: chronic fatigue, 63.0%; aggregate ACs, 35.3%; Sjögren's syndrome, 8.0%; IC, 3.0%; diabetes, 10.3%; and HLA-A*29, B*44 positivity, 9.7%. Prevalences of female sex; chronic fatigue; IC; and HLA-A*29, B*44 positivity were greater in patients with fibromyalgia. Logistic regression on fibromyalgia revealed three positive associations: chronic fatigue (p=0.0149; odds ratio 2.6 [95% confidence interval 1.2, 5.6]); Sjögren's syndrome (p=0.0004; 5.2 [2.1, 13.2]); and IC (p=0.0232; 5.7 [1.3, 25.7]). In an analysis of covariance, there were significant interactions of chronic fatigue, Sjögren's syndrome, and interstitial cystitis on fibromyalgia.*

Conclusion. *Fibromyalgia is common in non-Hispanic white adult index patients with primary immunodeficiency, especially women. Chronic fatigue, Sjögren's syndrome, and IC are significantly associated with fibromyalgia after adjustment for other independent variables.*

Introduction

Fibromyalgia is characterised by chronic widespread pain, tenderness, fatigue, sleep disturbances, impaired memory, and other manifestations in the absence of inflammation or damage to joints, muscles, or other tissues (1-3). There is no diagnostic laboratory test for fibromyalgia (2, 3). Fibromyalgia affects 2-8% of the adult population (2). The female:male ratio of fibromyalgia in the general adult population is 7:1 to 9:1 (4, 5).

Immunoglobulin (Ig) G subclass deficiency (IgGSD) and common variable immunodeficiency (CVID) are genetically and clinically heterogeneous primary immunodeficiency disorders characterised by frequent or severe bacterial infections of the respiratory tract and increased prevalence of autoimmune conditions (ACs) (6-10). In 2007, it was estimated that 250,000 persons in the US (1 in 1,200) had a diagnosed primary immunodeficiency disorder (including 9% IgGSD, 26% IgA deficiency, 35% CVID), among whom 7.2% had fibromyalgia (11). In series of adults with IgGSD, the female:male ratio was 1.3:1 to 7:1 (12-16). In 1,742 adults with CVID, the female: male ratio was 1.3:1 (17).

We conducted a retrospective analysis to determine the prevalence and clinical and laboratory associations of fibromyalgia in 300 consecutive adult index patients with IgGSD or CVID. We analysed these observations: age; sex; IgGSD; chronic fatigue; ACs; interstitial cystitis (IC); type 2 diabetes; body mass index (BMI); serum Ig isotype levels; total blood lymphocytes and subsets; and human leukocyte

antigen (HLA)-A and -B haplotypes. We compared characteristics of index patients with and without fibromyalgia and performed logistic regressions on fibromyalgia to identify significant independent associations. We discuss our results in the context of previous reports of fibromyalgia and related conditions.

Methods

Patient selection

The performance of this study was approved by the Institutional Review Board of Brookwood Medical Center and conducted in accordance with the Declaration of Helsinki. Informed consent was not required because the study is a retrospective analysis of observations from routine medical care. All patients: a) were non-Hispanic white adults from Alabama (≥18 years of age); b) had frequent or severe bacterial respiratory tract infections inadequately controlled by antibiotic therapy and other management; c) had IgGSD or CVID immunophenotypes; and d) were the first persons in their respective families diagnosed to have IgGSD or CVID (index patients). The present patients were referred during the interval 1996-2014.

Patient exclusions

We excluded patients with: a) hypogammaglobulinaemia attributed to B-cell neoplasms, organ transplantation, immunosuppressive therapy, anticancer treatment, or increased Ig loss; b) monoclonal gammopathy; c) human immunodeficiency virus infection; or d) incomplete evaluation. We also excluded patients with anaemia, iron, or vitamin B12 deficiency, hypo- or hyperthyroidism, sleep apnea, chronic heart disease, chronic lung disease (except allergic asthma), chronic demyelinating inflammatory polyneuropathy, and other non-fibromyalgia pain disorders.

Definition of primary immunodeficiency

IgGSD was diagnosed in accordance with the 1999 criteria of the Pan-American Group for Immunodeficiency and European Society for Immunodeficiencies (18) and the 2015 practice parameter for the diagnosis and management of primary immunodeficiency (19). We diagnosed CVID in accordance with the criteria of the 2015 International Consensus Document (20).

Definitions of other conditions

Fibromyalgia, ACs, IC, and diabetes were defined by referring physicians, our queries at initial consultation, and medication reviews. Each patient with fibromyalgia was diagnosed by a rheumatologist using ACR criteria that prevailed at the time (21). Dates of fibromyalgia diagnoses and use of 1990 or 2010 ACR diagnostic criteria (21) were not recorded in our past medical histories. ACs were diagnosed using criteria of the American College of Rheumatology (21). Chronic fatigue was defined as self-reported fatigue lasting more than six months that interfered with performing routine daily tasks, fulfilling employment responsibilities, and satisfying obligations of interpersonal relationships, without other explanation. Type 2 diabetes was classified according to the criteria of the American Diabetes Association (22). BMI was computed as kg/m^2 (23).

Laboratory methods

Testing was performed before IgG replacement therapy was initiated. Serum Ig levels were measured using standard clinical methods (Laboratory Corporation of America, Burlington, NC). We defined mean ± 2 SD as the normal or reference range for all Ig measurements, consistent with other studies (8, 24-26). Reference ranges for Igs are displayed in the footnote of Table I. Subnormal Ig levels were defined as those below the corresponding lower reference limits for age and were documented twice in all patients at times they did not have acute infections. We used values of the second IgG subclass measurements for the present analyses. Total blood lymphocytes were measured using a Cell-Dyn® 1500 or 1800 (Abbott Laboratories, Chicago, IL). Blood lymphocyte subsets were measured using flow cytometry (Laboratory Corporation of America, Burlington, NC). Reference ranges for lymphocytes and subsets are displayed in the footnotes of Table I. Subnormal lymphocytes and subsets were defined as those with levels below the corresponding lower reference limits.

HLA-A and -B alleles were detected using low-resolution DNA-based typing (polymerase chain reaction/sequence-specific oligonucleotide probe) in patients and family members to define haplotypes (8). HLA-A and -B haplotypes were determined in 751 unrelated white subjects from Alabama who were tested to establish paternity (controls) (27). Frequencies of the major HLA-A and -B haplotypes in control subjects were similar to those in Caucasians from a large national bone marrow donor programme (28). We evaluated positivity for HLA haplotypes A*01, B*08; A*02, B*44; A*03, B*07; and A*29, B*44 because these haplotypes occurred with greater frequency in Alabama non-Hispanic white index patients with IgGSD or CVID than control subjects (8, 10, 15, 16).

Statistics

The data set for analyses consisted of complete observations on 300 patients, except that HLA haplotypes were available for 167 patients (55.7%). IgG4 levels <1 mg/dL were imputed as 0.5 mg/dL. Age at diagnosis and BMI data were normally distributed and were compared using Student's *t*-test (two-tailed). Measures of serum Ig isotypes, total blood lymphocytes, and lymphocyte subsets were not normally distributed and were compared using the Mann-Whitney U-test.

Descriptive data are displayed as enumerations, percentages, mean ± 1 SD, median (range), or mean [95% confidence intervals (CI)]. Proportions were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. We computed odds ratios (OR) [95% CI] for some observations. We performed an initial logistic regression on fibromyalgia using these independent variables: age; sex; IgGSD; chronic fatigue; ACs; IC; diabetes; BMI; IgG subclasses; IgA; IgM; total blood lymphocytes; lymphocyte subsets; and positivity for HLA haplotypes A*01, B*08; A*02, B*44; A*03, B*07; and A*29, B*44. In a second logistic regression on

fibromyalgia, we deleted the independent variable ACs and substituted the variables Sjögren's syndrome; rheumatoid arthritis; Hashimoto's thyroiditis; Raynaud's phenomenon; and systemic lupus erythematosus. We performed an analysis of covariance to determine whether there were significant interactions of the independent variables chronic fatigue, Sjögren's syndrome, and IC on the dependent variable fibromyalgia. We defined *p*-values of <0.05 to be significant. Bonferroni corrections were applied to control the type I error rate at 0.05 for separate comparisons of continuous and dichotomous data, as appropriate. Analyses were performed with Excel 2000® (Microsoft Corp., Redmond, WA) and GB-Stat® (v. 10.0, 2003, Dynamic Microsystems, Inc., Silver Spring, MD).

Results

General characteristics

The mean age of 300 patients was 49 ± 12 (SD) y. There were 246 women (82.0%). IgGSD was diagnosed in 276 patients (92.0%). Chronic fatigue was reported by 189 patients (63.0%). ACs were diagnosed in 106 patients (35.3%). Nine patients (3.0%) had IC (Table I). Thirty-one patients (10.3%) had type 2 diabetes. Mean BMI was 28.9±7.0 kg/m^2.

Fifty-six patients (18.7%) had fibromyalgia (women:men 13:1). The prevalences of these characteristics were significantly greater in patients with fibromyalgia: female sex; chronic fatigue; IC; and positivity for HLA-A*29, B*44 (Table I). The prevalence of fibromyalgia in patients with CVID and IgGSD did not differ significantly (16.7% *vs*. 23.2%, respectively; *p*=0.5240).

Allergic asthma was diagnosed in 64 of 300 patients with immunodeficiency (21.3%). The prevalence of fibromyalgia did not differ significantly between patients with and without allergic asthma (18.8% *vs*. 18.6%, respectively; *p*=0.9846).

Median levels of IgG subclasses, IgA, and IgM did not differ significantly between patients with and without fibromyalgia (Table I). Median levels of total blood lymphocytes and lymphocyte subsets did not differ significantly between patients with and without fibromyalgia (Table I).

Positivity for each HLA-A and -B type did not differ significantly between patients with and without fibromyalgia. The prevalence of HLA-A*29, B*44 positivity was greater in patients with fibromyalgia (Table I). Six patients were homozygous for A*01, B*08. Three patients were homozygous for A*02, B*44. Homozygosity for A*02, B*15; A*03, B*07; A*11, B*07; and A*26, B*11 was observed in four respective patients.

Autoimmune conditions andinterstitial cystitis

We compared the prevalences of the six most common individual ACs and IC in patients with and without fibromyalgia. The prevalences of Sjögren's syndrome and IC were greater in patients with fibromyalgia (Table II).

Table I. Characteristics of 300 adult index patients with primary immunodeficiency.

Characteristic	Fibromyalgia (n=56)	No fibromyalgia (n=244)	*p*-value[1]
Mean age ± SD, y	50 ± 10	49 ± 13	0.8888
Male, % (n)	7.1 (4)	20.5 (50)	0.0190
IgGSD, % (n)	92.9 (52)	91.8 (224)	0.5240
Chronic fatigue, % (n)	82.1 (46)	58.6 (143)	0.0010
Autoimmune condition, % (n)*	51.8 (29)	31.6 (77)	0.0043
Interstitial cystitis, % (n)	10.7 (6)	1.2 (3)	0.0018
Diabetes, % (n)	3.6 (2)	11.9 (29)	0.0653
Mean BMI ± SD, kg/m^1	29.9 ± 6.3	28.6 ± 7.1	0.0910
Median IgG1, mg/dL (range)	408 (256, 676)	392 (95, 1460)	0.2194
Median IgG2, mg/dL (range)	224 (75, 702)	237 (17, 1650)	0.2702
Median IgG3, mg/dL (range)	32 (8, 85)	34 (17, 176)	0.0552
Median IgG4, mg/dL (range)	18 (0.5, 145)	13 (0.5, 139)	0.6718
Median IgA, mg/dL (range)	134 (32, 506)	151 (4, 555)	0.2032
Median IgM, mg/dL (range)	87 (4, 516)	95 (10, 511)	0.3590
Median blood lymphocytes x 10^3/μL (range)	1.9 (1.0, 4.2)	1.9 (0.4, 5.0)	0.7873
Median CD19$^+$ cells/μL (range)	224 (14, 979)	218 (2, 2340)	0.3860
Median CD3$^+$/CD4$^+$ cells/μL (range)	1034 (57, 2036)	914 (108, 2488)	0.1432
Median CD3$^+$/CD8$^+$ cells/μL (range)	358 (170, 1046)	415 (48, 1712)	0.1689
Median CD56$^+$/CD16$^+$ cells/μL (range)	141 (25, 407)	149 (4, 523)	0.3846
HLA-A*01, B*08 positivity, % (n)[2]	25.0 (14)	23.8 (55)	0.6933
HLA-A*02, B*44 positivity, % (n)[2]	26.8 (15)	18.9 (46)	0.1834
HLA-A*03, B*07 positivity, % (n)[2]	10.7 (6)	11.5 (28)	0.8713
HLA-A*29, B*44 positivity, % (n)[2]	26.8 (15)	5.7 (14)	<0.0001

SD: standard deviation; IgGSD: IgG subclass deficiency; CVID: common variable immunodeficiency; BMI: body mass index; HLA: human leukocyte antigen. Primary immunodeficiency was defined as IgGSD or CVID. Serum Ig reference ranges are: IgG 7.0-16.0 g/L (700-1600 mg/dL); IgG1 4.2-12.9 g/L (422-1292 mg/dL); IgG2 1.2-7.5 g/L (117-747 mg/dL); IgG3 0.4-1.3 g/L (41-129 mg/dL); IgG4 0-2.9 g/L (1-291 mg/dL); IgA 700-4000 mg/L (70-400 mg/dL); and IgM 400-2300 mg/L (40-230 mg/dL). IgG4 levels <1 mg/dL were imputed as 0.5 mg/dL. Blood lymphocyte reference ranges (mean ± 2 SD) are: total blood lymphocytes 0.6-4.1 x 10^3/μL; CD19$^+$ 12-645 cells/μL; CD3$^+$/CD4$^+$ 359-1,519 cells/μL; CD3$^+$/CD8$^+$ 109-897 cells/μL; and CD56$^+$/CD16$^+$ 24-406 cells/μL.

[1]These are nominal *p*-values. Bonferroni correction for 23 comparisons yielded a revised *p* for significance of <0.0022.

[2]HLA-A and -B haplotypes of 167 index patients were determined by family analyses. Inspection of HLA-A and -B types permitted exclusion of positivity for these haplotypes in the other 133 index patients.

Logistic regressions on fibromyalgia

In an initial regression, we used these independent variables: age; sex; IgGSD; chronic fatigue; ACs; IC; diabetes; BMI; IgG subclasses; IgA; IgM; total blood lymphocytes; lymphocyte subsets; and positivity for HLA haplotypes A*01, B*08; A*02, B*44; A*03, B*07; and A*29, B*44. There was a single positive association with fibromyalgia: chronic fatigue (*p*=0.0011; OR 3.4 [1.6, 7.2]). This model explained 7.0% of the variance of fibromyalgia (ANOVA *p* of regression <0.0041).

In a second regression, we used these independent variables: age; sex; IgGSD; chronic fatigue; Sjögren's syndrome; rheumatoid arthritis; Hashimoto's thyroiditis; Raynaud's phenomenon; systemic lupus erythematosus; IC; diabetes; BMI; IgG subclasses; IgA; IgM; total blood lymphocytes;

Table II. Autoimmune conditions and interstitial cystitis in 300 adult index patients with IgGSD or CVID.

Condition[1]	Fibromyalgia (n=56)	No fibromyalgia (n=244)	*p*-value[2]
Sjögren's syndrome, % (n)[3]	25.0 (14)	4.1 (10)	<0.0001
Interstitial cystitis, % (n)[4]	10.7 (6)	1.2 (3)	0.0018
Hashimoto's thyroiditis[5], % (n)	8.9 (5)	2.0 (5)	0.0097
Systemic lupus erythematosus, % (n)	8.9 (5)	4.1 (10)	0.1347
Mixed connective tissue disorder, % (n)	5.4 (3)	0.8 (2)	0.0467
Raynaud's phenomenon, % (n)	5.4 (3)	1.2 (3)	0.0812
Rheumatoid arthritis, % (n)	3.6 (2)	7.0 (17)	0.2748

IgGSD: IgG subclass deficiency; CVID: common variable immunodeficiency.
[1]These conditions were diagnosed before referral. Comparisons were made with Fisher's exact test or Pearson's chi-square test, as appropriate. Autoimmune conditions were diagnosed in 106 patients. Two or more autoimmune conditions were diagnosed in 37 of the 106 patients (34.9%). Each of these autoimmune conditions was diagnosed in one patient: alopecia areata; autoimmune haemolytic anaemia; Behçet's disease; Graves' disease; myasthenia gravis; polymyalgia rheumatica; sarcoidosis; and ulcerative colitis. Each of these conditions was diagnosed in two patients: anticardiolipin antibody syndrome; Crohn's disease; erythema nodosum; multiple sclerosis; pernicious anaemia; cutaneous psoriasis; temporal arteritis; and vitiligo. Three patients had autoimmune inflammatory arthritis not otherwise specified.
[2]These are nominal *p*-values. Bonferroni correction for 7 comparisons yielded a revised *p* for significance of <0.0071.
[3]Sjögren's syndrome occurred in 12 patients with and 12 patients without another autoimmune condition.
[4]Interstitial cystitis occurred in 7 patients with and 2 patients without an autoimmune condition.
[5]Hypothyroidism not otherwise specified was reported in 12 patients with and 33 patients without fibromyalgia (221.4% *vs*. 13.5%, respectively; *p*=0.1352).

lymphocyte subsets; and positivity for HLA haplotypes A*01, B*08; A*02, B*44; A*03, B*07; and A*29, B*44. There were three significant positive associations with fibromyalgia: chronic fatigue (*p*=0.0149; OR 2.6 [1.2, 5.6]); Sjögren's syndrome (*p*=0.0004; OR 5.2 [2.1, 13.2]); and IC (*p*=0.0232; OR 5.7 [1.3, 25.7]). This model explained 14.0% of the variance of fibromyalgia (ANOVA *p* of regression <0.0001).

Interaction of chronic fatigue, Sjögren's syndrome, and interstitial cystitis

The two logistic regressions above suggested that there is an interaction of chronic fatigue, Sjögren's syndrome, and IC on the dependent variable fibromyalgia. Using fibromyalgia as the dependent variable and chronic fatigue, Sjögren's syndrome and interstitial cystitis as independent variables in an analysis of covariance, the F-value was 6.5896 (*p*=0.0014). These results confirm that there are significant interactions of chronic fatigue, Sjögren's syndrome, and interstitial cystitis on fibromyalgia.

Discussion

The prevalence of fibromyalgia in the present patients (19%) was higher than the prevalence of fibromyalgia in the general adult population (2-8%) (2) and in persons in the US with diagnosed primary immunodeficiency disorders (7%) (11). Among the present patients with fibromyalgia, the ratio of women:men was 13:1, higher than the 7:1 to 9:1 female:male ratio of fibromyalgia in the general adult population (4, 5) and the 1.3:1 to 7:1 female:male ratio of adults with IgGSD or CVID (12-17).

Chronic fatigue, a characteristic of fibromyalgia (1-3), occurred in 82% of the present patients with fibromyalgia and was significantly associated with fibromyalgia after adjustment for other variables. Chronic fatigue was also reported by 59% of the present patients who did not have fibromyalgia. These observations suggest that chronic fatigue in some adults with primary immunodeficiency is due to undiagnosed fibromyalgia or non-fibromyalgia causes.

The prevalence of aggregate ACs was greater in the present patients with fibromyalgia. We observed a significant association of Sjögren's syndrome with fibromyalgia after adjustment for other independent variables. Widespread pain typical of fibromyalgia is common in patients with Sjögren's syndrome (29). Fibromyalgia occurs in 20–30% of persons with rheumatoid arthritis and systemic lupus erythematosus (30). These observations suggest that ACs contribute to the symptom complex classified as fibromyalgia in some adults.

IC was more common in the present patients with fibromyalgia and there was a significant positive association of IC with fibromyalgia after adjustment for other independent variables. In another study, there was a significant overlap in symptomatology of IC and fibromyalgia (31). Ig, including autoantibodies, is deposited within the bladder wall of some patients with IC, but this feature did not differ significantly from that of patients with non-IC urologic diagnoses (32). These observations suggest that the pathophysiology of IC and fibromyalgia symptoms is shared in some patients but cannot be attributed to Ig action in the bladder wall.

Median levels of IgG subclasses, IgA, and IgM did not differ significantly between the present patients with and without fibromyalgia. In a logistic regression on fibromyalgia, there was no significant association with serum IgG subclass, IgA, and IgM levels.

Total blood lymphocytes and lymphocyte subsets were not significantly associated with fibromyalgia in the present study. In two other reports, blood lymphocyte subsets did not differ significantly between patients with and without fibromyalgia (33, 34). In patients with fibromyalgia, numbers of CD25+ T-lymphocytes were decreased in one report (33) and elevated in another study (35).

The prevalence of HLA-A*29, B*44 positivity was greater in the present patients with fibromyalgia, but A*29, B*44 was not significantly associated with fibromyalgia after adjustment for other variables. Sibship analysis of 40 multi-case fibromyalgia families revealed linkage of fibromyalgia to the HLA region defined by HLA-A, -B, and -DRB1 alleles (36). In three other studies, the frequencies of HLA class I antigens or genotypes were similar in persons with fibromyalgia and in control subjects (37-39). HLA-DR4 positivity was more prevalent in patients with fibromyalgia than normal controls in one study (37), but the frequencies of HLA class II alleles in persons with

and without fibromyalgia were similar in two other reports (38, 39).

Infections may be involved in the pathogenesis of fibromyalgia (2, 40). By definition, all of the present patients, with or without fibromyalgia, had frequent or severe respiratory tract infections, typically sinusitis, bronchitis, and pneumonia (15, 16). It is presumed that most of these infections were caused by bacteria (10, 12, 15). In one study, the prevalence of fibromyalgia was greater among patients with hepatitis B virus infection than control subjects (41). In two other studies, there was no significant difference in fibromyalgia prevalence in persons with or without hepatitis B virus infection (41, 42). In patients with chronic hepatitis C, the prevalence of fibromyalgia did not differ significantly from that of control subjects (43). The prevalence of fibromyalgia was greater in persons with human immunodeficiency virus (HIV) than non-infected blood donors (44). Fibromyalgia occurred in some patients with parvovirus infection (45) and Lyme disease (46). These observations demonstrate associations of fibromyalgia and infections in some patients but do not establish that infections cause fibromyalgia.

The estimated prevalence of fibromyalgia in persons with HIV infections varied 29-fold across five studies: 1.3% (1/300) (47); 10.7% (15/140) (48); 14.1% (22/156) (49); 29.4% (15/51) (50); and 38.0% (38/100) (44). In the present study of patients with either CVID or IgGSD without HIV diagnoses, fibromyalgia was diagnosed in 18.7% (56/300). Thus, the prevalence of fibromyalgia in some studies of patients with HIV infection is greater than that reported in the present patients.

Uncertainties in the present work include the mechanisms by which chronic fatigue, Sjögren's syndrome, and IC interact in patients with fibromyalgia. Flow cytometry analysis of subsets of $CD19^+$, $CD3^+/CD4^+$ and $CD3^+/CD8^+$, and $CD56^+/CD16^+$ blood lymphocytes and functional studies of lymphocytes may have demonstrated abnormalities in the present cases. Because HLA types and haplotypes vary across geographic regions and race/ethnicity groups (51, 52), HLA characteristics of different fibromyalgia cohorts may be dissimilar. Our regression model explained 14% of the variance of fibromyalgia, indicating that factors not assessed in this study contribute to fibromyalgia pathogenesis. Symptoms decreased in a subset of patients with fibromyalgia treated with intravenous IgG in another report (53), but we have not evaluated the effects of intravenous IgG therapy in the present patients.

Conclusions

Fibromyalgia is common in non-Hispanic white adult index patients with IgGSD or CVID, especially women. Chronic fatigue, Sjögren's syndrome, and IC are significantly associated with fibromyalgia after adjustment for other independent variables.

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