fortune Journals

Research Article

FORTUNE JOURNAL OF RHEUMATOLOGY

ISSN: 2688-6766

Immunoglobulin Deficiencies in Rheumatoid Arthritis

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Abstract

Rheumatic diseases are more frequent in patients with immunoglobulin deficiencies than in those with intact humoral immunity. This study investigates the immunoglobulin profiles of 45 rheumatoid arthritis patients and 45 matched controls. Our analysis revealed a higher prevalence of IgE, IgA, and IgG subclass deficiencies in RA patients, especially among those with secondary autoimmune conditions. These immunoglobulin deficits may predispose to autoimmunity via impaired mucosal exclusion, altered cytokine signaling, and defective complement regulation.

Keywords: Rheumatoid arthritis; Immunoglobulin deficiency; IgE; IgA; IgG subclass; Autoimmunity; Cytokines; IgG4; Immunopathology; Class switch recombination.

Introduction

Rheumatic diseases are reported to be more common in patients with immunoglobulin deficiencies than in subjects with normal B cell function [1-3]. As an example, the prevalence of autoantibody production and rheumatoid manifestations have been documented to be unusually high in patients with common variable immunodeficiency and Bruton's agammaglobulinemia when compared to subjects with normal immunoglobulin levels [4-6]. Autoimmune disorders have also been reported to be more common in patients with selective IgA deficiency, the association being strongest for systemic lupus erythematosus, juvenile rheumatoid arthritis, rheumatoid arthritis, insulin-dependent diabetes mellitus, and myasthenia gravis [7-9]. In addition, about 20% of IgA- deficient patients have concomitant IgG subclass deficiencies, particularly in IgG2 and IgG4, and often present with autoimmune phenomena [10, 11]. Whereas IgG1 concentrations are frequently elevated in patients with a variety of autoimmune or connective tissue diseases, isolated deficiencies in other IgG subclasses have been reported to predispose to autoimmune and connective tissue disorders [12, 13]. The reason that autoimmune phenomena are more common in patients with immunoglobulin deficiencies is not known, but may reflect shared genetic factors [14-16], or impaired mucosal immunity [17-20]. We therefore examined the prevalence and pattern of immunoglobulin deficiencies in rheumatoid arthritis patients versus matched controls [21-24].

Materials and Methods

Subjects

Forty-five patients with rheumatoid arthritis were selected at random from the rheumatology practice of one of the authors (D.L.). A standardized form was used to review the history, physical findings, laboratory assessments

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Citation: J. Kelly Smith, David Lurie, Rhesa Dykes, Scott Reynolds, Karen Cantor, David Chi, and Steven Berk. Immunoglobulin Deficiencies in Rheumatoid Arthritis. Fortune Journal of Rheumatology. 7 (2025): 20-23.

Received: March 20, 2025
Accepted: March 26, 2025
Published: June 06, 2025

and therapy of each subject. Diagnoses were confirmed using the American Rheumatology Association criteria [25]. Autoimmune diseases were defined in accordance with Roitt [26]. After obtaining informed consent, venous blood was obtained, immediately processed, and the sera stored at –70°C for later processing. Forty-five age- and sex-matched control sera were provided by the American Red Cross from their blood donor pool. Medical histories were not available on these subjects.

All serum samples were assayed for IgE, IgG, IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgA1 and IgA2 [27].

Immunoglobulin Assays

Total serum IgE was measured using a Phadebas IgE paper immunosorbent test (PRIST) (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden). The detection range of this test is 0.5 to ≥800 kU IgE/L. For the purposes of this study, IgE deficiency is defined as an IgE level of <4.0 IU/mL (normal adult range in our laboratory is 4–79 IU/mL).

Serum levels of IgG, IgA, and IgM were measured by single radial immunodiffusion using Kallestad quantiplate/ Endoplate test kits (Sanofi Diagnostics Pasteur, Inc, Chaska, MN). Serum IgG subclasses were measured by single radial immunodiffusion using ICN kits (ICN Biochemicals, Irvine, CA). IgA subclasses were measured by single radial immunodiffusion using Bind A Rid kits (The Binding Site Limited, Birmingham, England).

Statistics

Statistical analysis was done using Statistica. Chi-square was used to analyze observed versus expected frequency of attributes. Probability testing was done using the 2-tailed Student's t test. The method of least squares was used for regression analysis. Percentages have been rounded off to the nearest whole number for readability.

Results

The mean age of patients was 60.4 ± 11.8 years (range 31–80), that of the controls 60.3 ±11.7 years (range 31–80). The study involved 31 women and 14 men. Forty-two percent of patients had one or more of the following organ-specific autoimmune diseases: primary myxedema (22.2%); secondary Sjogren's (20%); Grave's disease (4.4%), and insulin- dependent diabetes mellitus or pernicious anemia (2.2% each). The majority (89.5%) of these diseases occurred in women (p<.0001).

Eighty-seven percent of patients were taking nonsteroidal anti-inflammatory agents or aspirin. Eighty-four percent were receiving immunosuppressive therapy with one of the following regimens: prednisone (26.7%); prednisone plus methotrexate (22.2%); hydroxychloroquine (20%); methotrexate (11.1%); and prednisone plus hydroxychloroquine or penicillamine (2.2% each). Mean doses were 5.4 mg/day of prednisone (range 1–15 mg/day); 11.7 mg/week of methotrexate (range 7.5–17.5 mg/week); and 400 mg/day of hydroxychloroquine. An additional 28.9% of patients had received gold or hydroxychloroquine, 8.9% had received penicillamine, 6.7% had received methotrexate, and 2.2% had been treated with azathioprine or cyclophosphamide, but these medications were discontinued at least 6 months prior to entry in the study.

Mean values for IgA were significantly higher in rheumatology patients than in controls (p = .006). Patient levels of IgG1 and IgG3 were higher and IgG2 levels were lower than in controls, but the differences only approached statistical significance. One or more immunoglobulin isotypes were below normal in 44.4% of rheumatology patients and in 44.4% of controls. IgG4 and IgE deficiencies were the most common. Mixed deficiencies occurred in 17.8% of patients and 15.6% of controls. IgE deficiency was more prevalent in patients, while IgM deficiency was more common in controls with multiple deficiencies. IgG4 deficiency occurred with IgE deficiency in 50% of patients and in none of the controls (p<.0001). Immunosuppressive therapy did not affect the frequency of immunoglobulin deficiencies. Only 4 of 26 patients with uncomplicated RA had low immunoglobulin levels, whereas 16 of 19 with secondary autoimmune diseases did (p<.0001).

Discussion

In our prior study of 420 immunology patients, 46% of those with low IgE had autoimmune diseases compared to only 15% of those with normal or elevated IgE [21]. This finding is consistent with the current study, where IgE deficiency was more prevalent in RA patients, particularly those with multiple immunoglobulin deficiencies. Additionally, IgG4 deficiency appeared linked to IgE deficiency among patients, raising the possibility of a shared disruption in class switch recombination. The etiology of these deficiencies may involve dysregulation in cytokines such as IL-4 and IL-2, affecting immunoglobulin production [22-24]. IL-4 normally supports IgE and IgG4 synthesis, while IL-2 may inhibit this process. An imbalance favoring Th1 over Th2 cells might promote autoimmunity in RA. Furthermore, genetic elements like MHC haplotypes (e.g., HLA-A1, B8, DR3) and the IL-4 cytokine gene cluster on chromosome 11 may predispose individuals to both immunoglobulin deficiencies and autoimmune disease [14, 15, 34]. Immune responses to mucosal antigens, which would otherwise be blocked by IgA or IgE, may provoke systemic autoimmunity in their absence. Finally, the lack of inhibitory subclasses such as IgG4 may amplify complement activation by IgG1 and IgG3 immune complexes, contributing to inflammatory damage. The observed pattern of combined IgE, IgA1, and IgG4 deficiencies suggests that certain patients may be particularly susceptible to unregulated immune activation in RA.

Conclusion

Immunoglobulin deficiencies—especially those involving IgE, IgA, and IgG subclasses—are more common in patients with rheumatoid arthritis than in age- and sex-matched controls. These deficiencies appear to be linked to the presence of secondary autoimmune diseases and may reflect underlying genetic and immunological mechanisms affecting class switch recombination and cytokine signaling. Further genetic and functional studies are required to clarify the pathways linking immunoglobulin deficiencies to autoimmunity in RA.

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