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Original Research Article

Use of exploratory factor analysis to ascertain the correlation between the activities of rheumatoid arthritis and infection by human parvovirus B19

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ABSTRACT

Background and objective: We evaluated a possible correlation between the clinical activities of rheumatoid arthritis (RA) and human parvovirus B19 (B19) infection using exploratory factor analysis (EFA).

Materials and methods: RA patients were organized into two groups: 100 patients in the main group and 97 in the RA(DAS28) group. Four subgroups were defined from the main group according to the presence or absence of certain infection-specific markers: group I comprised 43 patients who had IgG antibodies against B19; group II, 25 patients with active B19 infection (B19-specific IgM antibodies and/or plasma viremia); group III, 19 patients with latent/persistent B19 infection (virus-specific sequences in peripheral blood leukocytes' DNA with or without B19-specific IgG antibodies), and group IV, 13 patients without infection markers. The RA(DAS28) group was divided into four subgroups similarly to the main group: group I, 35; group II, 31; group III, 19; and group IV, 12 patients. Disease-specific clinical values in both groups were analyzed employing EFA, and the RA(DAS28) group was additionally assessed using Disease Activity Score (DAS)28.

Results: RA activity was higher in patients who had markers of B19 infection. The highest activity of RA in both study groups was in patients with latent/persistent infection. In the RA(DAS28) group, according to DAS28, the highest activity of RA was in patients with active B19 infection.

Conclusions: Using EFA and DAS28, a correlation between the clinical activity of RA and B19 infection was confirmed. These data suggest that EFA is applicable for medico-biological studies.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by symmetrical, destructive polyarthritis and simultaneously by systemic inflammation that has a long-term impact on various organs, vessels and the hematopoietic system [1]. The exact cause of the rheumatoid process is not known. However, certain infections are considered to trigger autoimmunity and therefore are being studied in connection with RA.

Human parvovirus B19 (B19) has been observed to cause the initial immune response (i.e. the initial reaction preceding RA development in potentially receptive hosts) [2,3]. B19 infection is quite common in children and adults. It is usually asymptomatic but, if symptoms occur, they resemble those of the common cold. The infection presents with various manifestations that are well-known and covered extensively in the literature [4,5]. Evidence implicating B19 in RA causation is conflicting [6,7], but several reports have clearly confirmed its role in the pathogenesis of RA [8,9]. Thus, one can assume that infection by B19 has (at least in part) a role in disease activity that is directly (or sometimes implicitly) indicated by various clinical and laboratory data (both segregate and aggregate).

The present study was carried out to evaluate a possible correlation between the clinical activity of RA and human B19 infection using a statistical method known as exploratory factor analysis (EFA). EFA is efficient at reducing the dimensionality of the initial variables, eliminating outliers and retaining ''significant factors.'' In this case, the significant factors were the activity factors of RA. EFA was based partially on the data acquired within our previous study on the prevalence and clinical significance of parvovirus infection in RA patients [10].

Most clinical trials rely exclusively on the Disease Activity Score (DAS) [11,12] but we also explored another approach. One of the significant factors from the output of the EFA, a ''common factor,'' was assumed to be the aggravating factor of disease activity due to the statistical significance of the disease-specific clinical parameters it incorporated. The common factor was derived during the EFA so, unlike the DAS, it was native. However, to observe the objectivity of our study, the results of both approaches were evaluated and compared.

2. Materials and methods

The study protocol was approved by the Ethics Committee of Riga East Clinical University Hospital (Riga, Latvia). Each patient gave informed, voluntary, written consent to participate in this study.

2.1. Patients

The study featured two groups of RA patients: the main group and RA(DAS28) group. The main group was a cohort of 100 patients (72 women and 28 men; range, 21–81 years; mean, 55 years). The RA(DAS28) group comprised 97 RA patients (85 women and 12 men; range, 19–82 years; mean, 56 years). All patients fulfilled the current classification criteria for RA set by the American College of Rheumatology (ACR) [13]. Patients were hospitalized in the Rheumatology Department of Riga East Clinical University Hospital.

Initially, to exclude therapy as a co-factor of the activity of B19 infection, patients in the main group were divided into two subgroups [14]. The first group represented patients who had received various disease-modifying antirheumatic drugs and/or corticosteroids (68 RA patients). The second group comprised patients who had received only analgesics and/or non-steroidal anti-inflammatory drugs (32 RA patients). Elimination of another possible co-factor, disease duration, was essential, so 28 patients with early RA (i.e. with disease duration <2 years) were segregated from the main cohort.

Later, four subgroups were defined from the main group according to the presence or absence of certain infection-specific markers. The first subgroup (group I) comprised 43 patients who had suffered B19 infection and had IgG antibodies against B19. Group II comprised 25 patients with active B19 infection. They had IgM antibodies against B19 and/or B19 genomic sequences in plasma DNA samples. Group III comprised 19 patients with latent/persistent B19 infection. They had B19 genomic sequences in DNA isolated from peripheral blood leukocytes with or without IgG antibodies against B19. Group IV comprised 13 patients without infection markers and who were later termed ''virus-negative patients''. The RA(DAS28) group was (similar to the main group) divided into several subgroups according to the presence or absence of infection-specific markers. Thus, group I had 35 patients, group II had 31 patients, group III had 19 patients, and group IV had 12 patients.

2.2. Clinical and laboratory characteristics

All laboratory examinations were carried out using state-certified and standardized laboratory methods with appropriate equipment and reagents [14]. Each manifestation of the disease was evaluated by adhering to the corresponding identification standards [15]. Most RA-specific clinical parameters were selected based on our previous work [10] (though only some retained their utility for EFA). We evaluated the erythrocyte sedimentation rate (ESR; mm/h; Westergren method), tender and swollen joint counts (ACR 66/68-joint count), duration of morning stiffness (in h), level of C-reactive protein (CRP; mg/L); hemoglobin level (g/L), platelet count ($\times 10^9$/L), and lymphocyte count ($\times 10^9$/L).

Additionally, DAS28 was calculated using the standard formula for patients in the RA(DAS28) group. DAS28 $\leq$ 2.6 signified remission of RA; DAS28 $>$ 2.6 $\leq$ 3.2 indicated low disease activity, DAS28 $>$ 3.2 $\leq$ 5.1 indicated moderate disease activity, and DAS28 $>$ 5.1 indicated high disease activity.

2.3. Methods of viral diagnostics

IgG and IgM antibodies against B19 in plasma samples were identified using the VP2 enzymatic immunoassays developed by Biotrin (Dublin, Ireland) according to manufacturer protocols. Viral DNA was confirmed to be present by the nested