Prevalence of the hepatitis B virus markers among patients with ankylosing spondylitis and rheumatoid arthritis

ABSTRACT

Bulgaria is a country with the intermediate endemicity for hepatitis B virus (HBV) with predominance in adults between 40 and 49 years. Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are musculoskeletal conditions that cause severe long term pain and disability which prevalence increased with ageing. Reactivation of HBV is not rare event in patients receiving immunosuppressive therapy, but the prevalence of HBV markers among such patients is still unclear. The aim of the present work is to study distribution of two main HBV markers – HBV surface antigen (HbsAg), as marker for the present infection, and antibodies against HBV core antigen (anti-HBc), as a marker for past infection, among patients with AS and RA. The screening for HBV markers was done by commercial enzyme-linked assays for detection of HBsAg and anti-HBc in blood samples, in 14 sera samples concentration of HBV DNA were measured by quantitative real-time PCR. The study included 23 patients with AS and 24 with RA. Two (8%) of the patients with AS were positive for HBsAg and 9 (39%) - were anti-HBc positive. From patients with RA 2 (8%) were HBsAg positive and 7 (29%) – were anti-HBc positive. The presence of low HBV DNA concentration (between 182 copies/ml and <116 copies/ml) were established in 2 patients with AS. In conclusion the prevalence of markers for past HBV infection was high among patients with AS and RA, which is reason for more strict screening of patients before immunosuppressive therapy.

Keywords: hepatitis b virus, HBsAg, anti-HBc, ankylosing spondilitis, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) and ankylosing spondilitis (AS) are musculoskeletal conditions that cause severe long term pain and disability which prevalence increased with ageing. The prevalence of RA among adult population varies from 0.36% to 1% in different geographical regions with higher values for the north countries (Stoilov et al., 2011). In a genetically susceptible host HBV infection lead to the development of extrahepatic disorders such as polyarthritis and arthritis (Rong et al., 2007). At the same time immunosuppressive therapy with tumor necrosis factor-α inhibitors can induce HBV viral reactivation (Cantini et al.,...
2014) that is characterized by reappearance or the rise of viral DNA in a serum of patients with inactive or previously resolved HBV infection (Hoofnagle, 2009).

The geographic distribution of HBV infection is characterised with areas of high endemicity where the prevalence of HBV surface antigen (HBsAg) in the general population is over 7% these are South East Asia, China, Africa, the Middle East and the Amazon Basin; intermediate with prevalence between 2% to 7% - Eastern and Southern Europe, the Middle East, central Asia, South Asia, and parts of South America; and areas with low endemicity with up to 2% - North America, Northern and Western Europe and Australia (Owiti et al., 2015). For Bulgaria acute HBV infection is the second by prevalence (15.5%) following hepatitis A infection (77.12%) (Teoharov & Kevorkjan, 2014). Kojouharova et al. (2002), studying the main serological marker for HBV in the general population, established the prevalence of 3.87% for HBV surface antigen (HBsAg), and 23.59% for antibodies against HBsAg (anti-HBsAg) and against the HBV core antigen (anti-Hbc), which are markers for a resolved infection. The highest prevalence of 5.72% for HBsAg was detected in adults aged between 40 and 49 years (Kojouharova et al., 2002).

The aim of the present work is to study distribution of two main HBV markers – HBV surface antigen, as a marker for the present infection, and antibodies against HBV core antigen, as a marker for past infection, among patients with AS and RA.

Materials and Methods

Patients: The study started in January 2015 and included 47 patients, who were diagnosed at Clinic of rheumatology of University Hospital for Active Treatment “St. Ivan Rilski” – Sofia with AS - according to the modified New York criteria (Van der Linden et al., 1984), and with RA according to American College Rheumatology criteria 1987 (Arnett et al., 1988). Variables, as patient’s age and disease duration, are labeled as mean±standart deviation (SD). The ethics committee of Medical University, Sofia approved the protocol for this study, and informed consent was obtained from all patients.

Serological and virological evolution for HBV: Testing of the sera was performed at the NRL of Viral hepatitis of National Center of Infectious and Parasitic Diseases, Sofia. Sera samples from all patients were tested by enzyme-linked immunosorbent assay (ELISA) for the presence of HBsAg (SURASE B-96 ELISA kit GmbH, Germany) and anti-HBc (Competitive ELISA for HBCAb in human serum and plasma, DIA.PRO, Italy) according manufacturer instructions.

Serum HBV viral load was determined by COBAS AmpliPrep/COBAS TaqMan HBV Test (Roche Diagnostics GmbH), with an analytical measurement range from < 2.00E + 01 IU/ml to > 1.70E + 08 IU/ml. The conversion factor between HBV copies/ml and HBV IU/ml is 5.82 copies/IU, using the WHO International Standard for HBV DNA for nucleic acid technology assays testing – NIBSC 97/746.

Results

The target cohort included 47 patients in age from 19 to 69 years, with a 50±13 years mean age. The main patient’s characteristics - demographic data and information regarding applied therapy, were shown on Figure 1.

The time between the appearance of the first symptom and the diagnosis was between 1.5 and 37 years. Disease activity score (DAS) varied from 0.6 to 7.57, where for the AS in case of DAS <1.3 disease was defined as inactive and for RA values <2.6 were considered consistent with remission. The magnitudes of the parameters over these cut off values signified disease activity. From all patients 17 (36%) were positive for at least one HBV marker – HBsAg, anti-HBc or HBV DNA. To evaluate the prevalence of HBV infection the target cohort was subdivided at two groups: patients with AS and patients with RA. Forty nine percent
(49%) of the patients were diagnosed with AS and 51% – with RA.

**HBV markers in patients with AS**

Twenty tree patients (49%) were diagnosed with AS (AS-patients) with a mean age of 44±12.3 years. From them 12 (52%) were male and 11 (48%) were females. Disease duration varied from 3.0 to 37.0 years with the mean value of 18.2±8.7. Thirteen of the patients AS were treated symptomatically with non-steroidal anti-inflammatory drugs and chondroitin sulfate, and 10 of patients were treated with synthetic or biological disease-modifying antirheumatoid drugs (DMARDs). Two AS-patients (8%) were positive for HBsAg, and after testing of anti-HBcIgM were with negative result and that exclude acute HBV infection.

From all patient 23 AS-patients 9 (39%) were positive for the anti-HBc IgG antibodies (past HBV infection) (Table 1).

**Table 1. Distribution of HBV serological markers among AS- and RA-patients.**

<table>
<thead>
<tr>
<th></th>
<th>AS (%)</th>
<th>RA (%)</th>
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<tbody>
<tr>
<td>(n=23)</td>
<td>(n=24)</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>9 (39%)</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>HBsAg/anti-HBc</td>
<td>2 (20%)</td>
<td>2 (28%)</td>
</tr>
<tr>
<td>(n=10)</td>
<td>(n=7)</td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>2 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>(n=5)</td>
<td>(n=9)</td>
<td></td>
</tr>
</tbody>
</table>

HBsAg – hepatitis B surface antigen; anti-HBc – antibodies against hepatitis B core antigen

Two HBsAg positive patients were and anti-HBc IgG positive. Five AS-patients were tested for HBV DNA and 2 of them were positive - one patient was HBsAg- and anti-HBc IgG-positive, and the second patient – was HBsAg- and anti-HBc IgG-negative. The concentration of HBV DNA was 182 copies/ml and <116 copies/ml respectively.

**HBV markers in patients with RA**

From all patients, 24 (51%) were diagnosed with RA (RA-patients). The mean age of this group was 55±12.1, with a maximum age of 69 years. Four RA-patients (17%) were male and 20 (83%) – female. Disease duration varied from 1.5 to 69.0 years with the mean value of 6.8±7 years. Half of the patients were treated symptomatically and the other 12 – with synthetic or biological DMARDs. Two (8%) from the patients with RA were positive for HBsAg, but they were not with acute HBV infection. Seven patients (29%) were with past HBV infection - they were anti-HBc IgG positive (Table 1). In 9 RA-patients concentration of HBV DNA were measured and all were negative.

**Discussion**

HBV infection may present with different extrahepatic manifestation, such as rheumatoid arthritis, and may have a role in pathogenesis of autoimmune diseases (Yilmaz et al., 2014). The autoimmunity can be induced via different virus mechanisms, such as molecular mimicry, bystander activation and epitope spreading (Varache et al., 2011). Despite Bulgaria is a country with intermediate endemicity (< 7%) of HBV infection the real prevalence of this infection is not known in patients with AS and RA. A study of the prevalence of HBV markers began on January 2015 year and includes 47 patients from the Clinic of Rheumatology of University Hospital for Active Treatment “St. Ivan Rilski” – Sofia. Patients were divided into two groups - with diagnosis of AS and with RA. The mean age of the two groups was 44±12.3 and 55±12.1 years with disease duration of 18.2±8.7 and 6.8±7 years, respectively. The prevalence of HBsAg among two patient groups was 8%, which is not so higher than the prevalence of the same HBV marker (5.72%) among the general Bulgarian population of similar age (Teoharov & Kevorkjan, 2014). The difference can be explained with the low number of studied patients – 23 and 24 respectively, compared with number of 11 597 persons from the general population. Despite this limitation of our study in combination with the long duration from the onset of arthritic diseases, the results provide evidence against major role of HBV viral infection in the pathogenesis of AS and RA. The HBV DNA, with low concentration, has been detected only in one HBsAg positive patient, which is the evidence of chronicified HBV infection. The prospective longitudinal study in France of ESPOIR cohort of adults with possible early RA who are ≥18 and <70 years old revealed the HBsAg prevalence of 0.65%, which is comparable with the prevalence in general population for this geographical region (Varache et al., 2011). Higher prevalence of HBsAg among patients with AS was established for China population, but this is explained with their high frequency of HLA-B27 gene (Zheng et al., 2012).

For the second HBV marker – anti-HBc, the high prevalence of 39% for patients with AS and of 29% - for patients with RA were established. The prevalence of markers for past HBV infection in the general population is
35% of the age group from 40 to 49 years and 34.23% for age group from 50 to 59 years (Teoharov & Kevorkjan, 2014). The prevalence of past HBV infection among patients with RA is almost similar according to the general population, but for patients with AS the prevalence of anti-HBc was higher.

The significance of the proposed study is connected with possible reactivation of HBV virus during the treatment of AS and RA. The corticosteroids may increase the expression of HBV through a glucocorticoid responsive element, which has been detected in the viral genome, and stimulates viral replication in patients under these treatments. The use of anti-tumor necrosis factor drugs may result in an increase of HBV replication in patients under these treatments. The use of antitumor necrosis factor drugs may result in an increase of HBV viral replication. And very often reactivation occurs months after the withdrawal of immunosuppressive therapy (Lopez-Serrano et al., 2015). Proposed results are part of study of HBV reactivation during treatment of patients with ankylosing spondylitis and rheumatoid arthritis. In conclusion the high prevalence of markers for past HBV infection among patients with AS and RA is a reason for more strict screening before the start of the treatment.

Acknowledgments

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References


