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THE ASSOCİATİON BETWEEN RHEUMATOİD ARTHRİTİS AND ANKYLOSİNG SPONDYLİTİS WİTH HEPATİTİS B AND C VİRUSES

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ABSTRACT

Objective: To study the association of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) diseases with HBV and HCV viruses together with etiopathogenesis, concomitance, differential diagnosis and treatment. Materials and Method: The study included 101 RA and 117 AS patients. Two different control groups comprised 113 subjects for the RA group and 94 for the AS group. All patient records were retrospectively reviewed for serological status. Demographic characteristics, duration of disease and treatment regimens were noted. To evaluate disease activity, serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were recorded. HBs Ag, HBs Ab and anti-HCV screening was performed in all patients. Patients positive for HBs Ag were tested for HBe Ag, HBe Ab, HBc Ag, HBc Ab, HBV–DNA parameters. Anti HCV positive patients were tested for HCV-RNA. All positive ratios were compared with the RA, AS and control groups. Results: The mean age was 51.9±12.6 years and 38.4±11.1 years in patients with RA and AS, respectively. HBs Ag prevalence of 1.9% (2/101) was found in the RA group. There was no statistically significant difference in the RA group compared with the control group. Positive results in HBs Ag and/or HBs Ab were assessed as viral contact. HBs Ag and/or HBs Ab positivity prevalence of 37.6% (38/101) was found in the RA group. There was no statistically significant difference in the RA group compared with the control group. Anti HCV prevalence of 0.9% (1/101) was found in the RA group. There was no statistically significant difference in the RA group compared with the control group. HBs Ag prevalence of 6% (7/117) was found in the AS group. There was no statistically significant difference in the AS group compared with the control group. HBs Ag and/or HBs Ab prevalence of 46.1% (54/117) was found in the AS group. There was no statistically significant difference in the AS group compared with the control group. Anti-HCV positivity prevalence of 0.9% (1/117) was found in the AS group. There was no statistically significant difference in the AS group compared with the control group. Conclusion: RA and AS diseases are firmly associated with HBV and HCV viruses in respect of defining etiopathogenesis, concordance, differential diagnosis and treatment regimens. In this study, it was aimed to clarify this association. Further studies are necessary for better understanding.

KEYWORDS: Rheumatoid arthritis, hepatitis B virus, hepatitis C virus, ankylosing spondylitis,

INTRODUCTION

The etiopathogenesis of many rheumatismal diseases is still not fully understood. The predominant view is that the disease has developed with environmental factors on a genetic predisposition. The primary of these factors is viruses. That a high level of antiviral antibodies has been found in the serum of patients with rheumatism and viral antigens have been determined in the target tissue supports this view.[1]

Rheumatoid arthritis (RA), is a chronic inflammatory systemic disease characterised by symmetrical, erosive synovitis especially involving diarthrodial joints, in which severe deformities and disabilities may develop. Genetic, environmental, bacterial, viral and immunological factors are emphasized in the etiopathogenesis.[1,2]

Ankylosing spondylitis (AS) is a member of the heterogenous disease family known as spondyloarthropathies (SpA). SpA is a chronic inflammatory disease group of heterogenous character, which may involve sacroiliac joints, the axial skeleton, peripheral joints to a lesser degree, and apart from joints, organs such as the eyes, skin and the cardiovascular (CVS) system. The etiology is unknown but includes the interaction between environmental and genetic factors.[3]

Hepatitis B virus (HBV) is a double-stranded DNA virus which is a member of the hepadna virus family. The

HBV virus affects a large proportion of the global population, primarily in developing countries. Clinically, HBV may be encountered with many extra-hepatic findings.[4]

Hepatitis C virus (HCV) is a single-strand RNA virus of the Flaviviridae family. There are 6 major genotypes. In addition to being a hepatic disease agent, HCV is related to heamatological, renal, dermatological, rheumatological and autoimmune diseases involving many systems. HCV-related rheumatismal diseases may include often seen symptoms of arthralgia, arthritis and vasculitis, mixed cryoglobulinemia, fibromyalgia and Raynaud's phenomenon.[5-7]

Within rheumatismal diseases, the clinical findings of RA and AS diseases to which HBV and HCV viruses have led, may be confused with each other in many situations. Therefore, many differentiating laboratory tests and imaging methods are used.[5,6]

Care must be taken in the use of several immunosuppressive agents which are administered in the treatment of rheumatismal diseases as they may lead to both liver toxicity and virus replication. Biological agents used in recent years may lead to viral replication in particular. Therefore, close monitoring is required throughout the treatment period.[1-3]

Clinical differentiation is extremely important in the diagnosis and organisation of treatment for these diseases. In addition, it must not be forgotten that RA or AS and viral hepatitis could be seen together in the same individual with causes often seen in the population.

In this study, the combination of viral B and C hepatitis in patients presenting with RA or AS was researched. In the study, attention was drawn to both the role of these viruses in the etiology of rheumatismal diseases and the common findings which can be clinically confused. In addition to clinical differentiation, it was researched as to how useful laboratory and imaging methods could be. It was hoped that the results of this study would contribute to the clarification of the relationship between RA and AS diseases and viral B and C hepatitis.

MATERIAL AND METHOD

The study included a total of 117 patients diagnosed with AS according to the Modified New York criteria and 101 patients diagnosed with RA according to the ACR 1987 criteria between January 2009 and February 2010. Patient records were retrospectively evaluated in respect of hepatitis serology.[8,9]

Study Inclusion Criteria: male and female patients aged 18-80 years, diagnosed with RA according to ACR 1987 criteria or diagnosed with AS according to 1984 Modified New York criteria.

Study Exclusion Criteria: the presence of connective tissue disease other than RA and AS, primary liver disease, malignancy, lymphoproliferative disease, a history of long-term intravenous medication use, pregnancy or a history of frequent blood transfusions.

The control groups were selected to be close to the patients, with similar age distributions as 113 individuals for the RA control group and 94 individuals for the AS control group.

A record was made of the patient demographic characteristics, duration of disease and treatment protocols applied. Examination was made of the locomotor system of all the patients. In respect of disease activity, acute phase reactants and rheumatoid factor (RF) values were examined.

Approval for the study was granted by the Local Ethics Committee and informed consent was obtained from all participants. The study was applied according to the Helsinki Declaration.

Statistical Analysis

Evaluation of the data was made using SPSS 15.0 statistics software. Results were stated as mean ±standard deviation. The Chi-square test was used in the comparisons. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The RA group patients were 74 (73.3%) females and 27 (26.7%) males with a mean age of 51.9±12.6 years. The AS group patients were 20 (17.1%) females and 97 (82.9%) males with a mean age of 38.4±11.1 years. The demographic characteristics of the patients are shown in Table 1.

Table 1.

HBs Ag positivity was determined in 2 (1.9%) patients in the RA group and 7 (6%) patients in the AS group. Anti-HCV positivity was determined in 1 (0.9%) patient in the RA group and 1 (0.8%) patient in the AS group. In the RA patient the HCV-RNA value was 235,000 copy/ml and in the AS patient, the value was 0.

In the total 9 patients determined with HBs Ag positivity, other HBV-related serological parameters were examined. In 1 RA patient, HBeAb positive, HBe Ag negative, HBc IgG and HBc IgM negative were determined. In 1 AS patient, HBe Ag negativ, HBe Ab positive and HBc IgG negative were determined.

HBs Ag positivity was determined at 1.9% (2/101) in the RA patient group and at 5.3% (6/113) in the control group. No statistically significant difference was determined between the groups ($p>0.05$).

The 2 RA patients with Hbs Ag positivity were both female. One had positive RF value (624,000 IU/ml), and a normal level of liver enzymes. The other patient had positive RF value (97 IU/ml) and liver enzymes within

normal limits. Neither patient was receiving antiviral treatment.

HBs Ab positivity was determined at 35.6% (36/101) in the RA patient group and at 38.9% (44/113) in the control group. No statistically significant difference was determined between the groups (p>0.05).

HBs Ag or HBs Ag positivity was determined at 37.6% (38/101) in the RA patient group and at 44.2% (50/113) in the control group. No statistically significant difference was determined between the groups (p>0.05).

When the RA patient group was examined in respect of HCV serology, the anti-HCV positivity rate was 0.9% (1/101) in the RA group and 1.8% (2/113) in the control group. No statistically significant difference was determined between the groups (p>0.05).

The RA patient with anti-HCV positivity was a 54-year old female with normal levels of liver enzymes. Before treatment the viral load value was 235,000 copy/ml. As anti-rheumatismal medication, low-dose methylprednisolone was administered and as antiviral treatment, interferon and lamivudine. In the follow-up, a reduction was seen in the HCV-RNA level to 14,000 copy/ml. Cyclical increases were determined in the liver enzymes. As clinically active arthritis was determined, low-dose steroid treatment of hydroxychloroquine (HQ) was added.

HBs Ag positivity was determined at 6% (7/117) in the AS patient group and at 2.1% (2/94) in the control group. No statistically significant difference was determined between the groups (p>0.05). HBs Ab positivity was determined at 40.1% (47/117) in the AS patient group and at 43.6% (41/94) in the control group. No statistically significant difference was determined between the groups (p>0.05).

The AS patients determined with HBs Ag positivity were 1 female and 6 males. Of these patients, 3 were taking biological agents, 3 were taking sulfasalazine (SLZ)and non-steroid anti-inflammatory drugs (NSAID), and the other patient was taking SLZ, NSAID and methotrexate (MTX). Raised levels of liver enzymes were not determined in any patient. The HBV-DNA values were determined as 0 in 2 patients.

HBs Ag or HBs AB positivity was determined at 46.1% (54/117) in the AS patient group and at 46.8% (44/94) in the control group. No statistically significant difference was determined between the groups (p>0.05).

Anti-HCV positivity was determined at 0.9% (1/117) in the AS patient group and at 2.1% (2/94) in the control group. No statistically significant difference was determined between the groups (p>0.05).

The anti-HCV positive AS patient was female with negative RF value and liver enzymes within normal levels. The HCV-RNA value was 0 copy/ml and SLZ was used as medication. In the follow-up no increase was determined in viral loading or liver enzyme levels. From the hospital records it was determined that no antiviral agent was used and Brucellosis treatment was applied by the Infectious Diseases Clinic.

Table 1: Demographic characteristics of the patients.

Disease	RA (n=101)	AS (n=117)
Age	51.9 ± 12.6	38.4 ± 11.1
Gender F /M	74/27 (73.3%/26.7%)	20/97 (17.1%/82.9%)
Height (cm)	161.1 ± 6.1	169.6 ± 8.1
Weight (kg)	70.3 ± 12.6	71.1 ± 10.1

DISCUSSION

RA and AS diseases cause a weakening of immunity because of both the etiopathogenesis and the treatment administered. This patient group has no defence agains several diseases. When the infection pathways and risk factors of HBV and HCV viruses are considered, RA and AS patients are seen to encounter these viruses at a higher rate than the normal population due to frequently being in a hospital environment and the immunosuppressive treatment regimes.[1-3]

HBV and HCV viruses, which may be confused with several rheumatismal diseases, can lead to different clinical tables. Clinical differentiation from RA and AS diseases may be difficult. In addition, for a long time the focus has been on the infection agents in the etiology of these two disease groups. Several studies have been made to investigate the relationship between viral hepatitis agents and rheumatsimal diseases.[5-7]

In a study by Tanasesau et al[10], the relationship was investigated between some connective tissue diseases and HBV and HCV viruses. A higher prevalence of HBV was determined in SpA patients with HLA B27 positivity and it was concluded that the disease could develop with the HBV virus settling on a genetic predisposition.

With the development of molecular technology, rheumatismal findings in infectious diseases are more quickly diagnosed and understood. From a scan of literature in the period January 2008 – January 2010, there are many studies supporting the role of persistent viral and bacterial infections in RA or the development of similar symptoms.[11]

In a 2009 study by Kurbanov et al[12], serological parameters were examined in 202 RA patients and 200 healthy control subjects in respect of herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein Barr virus (EBV), HBV, HCV and human T-cell leukaemia virus (HTLV) 1 and HTLV 2. The study concluded that

HBV, HTLV 1 and HTLV 2 antibodies in the patients were found to be at the same level as in the normal population, and EBV, CMV and HSV antibodies were determined at a higher level in the RA patient group. This result supports the view that chronic infection associated with HSV and EBV viruses leads to an autoimmune reaction which plays a role in the etiology of RA.

In 1843 Robert Graves defined the relationship between hepatitis and arthritis as 'patients who develop inflammation in the joints together with jaundice will suffer an attack of liver hepatitis and urticaria will follow'.[13] It is known that HBV itself and immunization against HBV lead to a clinical path similar to RA. The relationship between HBV and RA was first revealed with HBs Ag determined in the synovium of RA patients.[5-8]

Chronic B viral hepatitis can cause findings related to the musculoskeletal system in addition to liver disease. HBV-related arthritis is generally polyarticular and besides the involvement of large joints, small joint involvement is observed similar to RA. Immunocomplexes from the development of arthritis are held responsible.[14,15]

In a study by Karatay et al[16] of 20 RA patients, 26 AS patients and 56 healthy control subjects, HBV was determined at a statistically significantly higher rate in the RA group compared to the control group. It was concluded that HBV could play a role in the etiology of RA.

RA and AS patients are a high-risk group for HBV from the disease itself, from the immunosuppressive medications used and also from frequent exposure to the hospital environment. For these reasons, exposure to the HBV virus would be expected to be higher in RA patients. In the current study, the control group was formed of relatives of the patients who presented at the polyclinic. That there was no difference between the two groups could be related to diseases not having been given in full in the anamnesis and the hiding of hepatitis-related diseases. Unfortunately, in Turkish society, patients diagnosed with hepatitis and their relatives have insufficient information about diseases and contagion pathways. Viral hepatitis is a significant infection which can be a public health threat.

In Turkey, the prevalence of exposure to HBV has been reported at rates of 17-40%[4]. If positivity in any one of the HBV viral parameters is considered as exposure to the virus, the positivity rate of the RA patient group to one of the HBV viral parameters at 37.6% (38/101) and of the AS patient group at 46.1% were found to be statistically significantly high compared to the normal population. In addition, high rates of exposure to the virus were found at 44.2% in the RA group and at 46.8% in the AS group. In both the patient group and the control group of the current study, this was found to be a high proportion compared to the normal population.

In conclusion, exposure to HBV in both the patient and control groups of the current study was found to be high compared to the general population. This result can be associated with chronic diseases, the treatments adminstered, exposure to a hospital environment, concomitant diseases, not revealing viral infections which were present in addition to the patients included in the study being of a very advanced age group.

In patients previously infected with HBV virus, HBV reactivation may develop with rheumatismal diseases, malignancy, autoimmune hepatitis, immunosuppressive therapy or chemotherapy. While HBV reactivation has been reported as 7.3% in chronic HBV infection, this rate reaches 14-50% in those receiving immunosuppressive therapy. Within immunosupprssive therapies, corticosteroid treatment in particular leads to reactivation at a high rate. This is explained by it containing the element which responds to HBV-DNA. Patients with HBs Ag positivity are chronic carriers. Therefore, antiviral therapy prophylaxis is recommended for these patients 1 week before starting immunosuppressive therapy or chemotherapy and for at least 6 months afterwards.[17] Lamivudine was the main prophylaxis agent used in this study as it provides a rapid drop in HBV replication in the first weeks and this effect last for several years. However, it must be kept in mind that resistance may develop to lamivudine with long-term use. In a study by Kalyoncu et al, lamivudine therapy was determined to be safe, well-tolerated and effective in patients with chronic HBV infection who were undergoing immunosuppressive treatment.[18]

In recent years, the most valuable test has been seen to be anti-cyclic citruline peptide (anti-CCP), which is a marker with sensitivity equal to RF and high specificity. This raises the question of whether there is a relationship between HBV and anti-CCP. In contrast to RF, anti-CCP positivity is rarely encountered in patients with chronic B viral hepatitis and extra-articular involvement. Therefore, it can be said that anti-CCP is a useful test in the differentiation of chronic B viral hepatitis and RA diseases. In the current study, 2 HBs Ag positive RA patients had a positive anti-CCP test.[19]

AS is a member of the heterogenous disease family known as SpA. Several studies have been conducted focusing on the relationship between environmental factors and HLA B27 gene in the etiology of AS. The views related to HLA B27 are that HLA B27 antigene may have a role as an infection agent, HLA B27 may be an indicator of an immune response gene confirming an environmental trigger factor, HLA B27 may create tolerance in the formation of the reacton against foreign antigens and HLA may increase neutrophil activity.[3,9,12]

The close relationship of AS with HLA B27 genotype is the reason for the emphasis on the pathogenic role of this gene. As a result of previous studies, a relationship has been revealed between HLA B27 and various pathogens, the most frequently emphasised allele being HLA B2705. One of these is the similarity between Klebsiella nitrogenase enzyme and HLA B27 allele. From this starting point, it is thought that in the settling of the genetic tendency of the bacteria, the gastrointestinal route is invaded, which is thought to lead to chronic inflammation and an increase in permeability. With time, these bacterial arthritogenic peptides reach the joints via the bloodstream. The localisaton of the enthesis regions can be explained by the affinity with bacterial antigens.[20]

Previous studies on the correlation between the global distribution of HLA B27 and auto-immune and infectious diseases have concluded that HLA B27 is seen less often in regions of endemic malaria, which has led to research into the relationship between this genotype and plasmodium falsiparum bacteria. It has been concluded that HLA B27 genes are protective against malaria.[21]

It has been observed that in AS patients with viral B hepatitis, an adequate immune response does not develop due to the immunosuppressive treatment applied and there is a higher tendency to be an HBV carrier (HBs Ag positive, HBs Ab negative).[22]

HCV may be encountered with many systemic findings apart from just being a hepatitis agent. HCV involvement other than the liver is most frequently seen in the joints at the rate of 20%. HCV joint involvement may be seen in 2 forms. The first is symmetrical polyarthritis similar to RA involving the small joints of the hands and feet. The second form is mono-oligoarthritis of intermittent character in mid and large joints. The first form is difficult to differentiate from early stage RA. In fact, HCV polyarthritis similar to RA completely meets the RA diagnostic criteria according to the 1987 ACR criteria.[23] When erosion is not seen, various laboratory tests are required to differentiate from early stage RA. Previous studies have reported RF positivity in 90% of RA patients and in 81% of HCV polyarthritis cases. Just as in antibodies outside several organs, HCV leads to RF reactivity. With increased joint involvement, so RF reactivity increases. Therefore, RF is not sufficient to differentiate these two clinical conditions.[11,12,13]

Anti-CCP, which is seen as a second generation test, has been reported to have rates of positivity of 83% in RA patients and 4.5% in patients with HCV polyarthropathy. Although anti-CCP has comparable sensitivity with RF (83%, 90%), specificity has been found to be higher (95%, 18%). In contrast to RA, HCV polyarthritis which is similar to RA has a benign course and does not lead to joint erosions or deformities.[25] With correct diagnosis, immunosuppressive medications with significant toxicity for the liver should not be used.

In the current study, a female RA patient determined with HCV positivity was determined not to carry any risk factor for parenteral contagion pathway. There was no HCV carrier in the family. The patient was reconsidered in respect of the diagnosis. Clinically, there was erosive arthritis in the hand and elbow joints. There was stiffness in the mornings for more than one hour. In the laboratory tests, RF was determined as 130mg/dl and the anti-CCP test was positive. In the liver biopsy, viral RNA of 235,000 copy/ml was determined. The diagnosis of RA was confirmed. In addition to the low-dose steroid treatment, interferon (IFN) and ribavirin were started.

In recent years, anti-TNFs have been of great importance in RA and AS treatment. TNF-α plays a key role in viral clearance. Therefore, it should be taken into account that anti-TNF agents can increase HBV and HCV replication and viral parameters must be examined before treatment.[11]

In previous studies of patients who have gained immunity by contracting HBV viral hepatitis, it has been concluded that biological agents can be safely used on these patients. However, in those with low titre HBs Ab, it has been observed that together with an increase in the viral load after anti-TNF treatment, there was a greater fall in HBs Ab levels. Therefore, close monitoring is required for those with low HBs Ab titre.[25] The HBs Ag positive RA patient in the current study had been using Etanercept for 3 years and in the follow-up no increase was determined in liver enzymes or viral load.

Studies have shown that RA patients not developing a sufficient immune response when in contact with HBV and the tendency to be carriers is associated with the immunosuppressive agents used in RA treatment.[22,23,25] Immunity is not a concern for HCV. Therefore, serology scanning for HBV and HCV should be applied to every RA patient and if there is no immunity, immunization should be performed befor treatment against HBV. When HBV or HCV viral hepatitis is determined, it is necessary to re-assess not only the treatment regime but also the diagnosis, because the extra-hepatic findings of both HBV and HCV may be clinically confused with RA.

Many agents administered in AS treatment are toxic to the liver. Therefore, viral parameters and liver enzymes must be examined before treatment. In addition, it should be kept in mind that these two diseases can be found together and the treatment adminstered can exacerbate an existing viral disease.

In many previous studies, in inactive HBV carrier RA or AS patients, an increase has been determined in viral DNA load and liver enzymes in the follow-up after anti-TNF treatment. Viral load and liver enzymes were seen to return to normal levels following treatment of lamivudine 100mg/day. Therefore, for HBV carriers, it is

recommended that prophylactic antiviral treatment is started before anti-TNF.[14,15,19,22]

In conclusion, different clinical findings of HBV and HCV viruses may be encountered and these two viral hepatitis agents which are frequently seen in patients with rheumatism in our society, should be kept in mind. In addition, as these viral hepatitis diseases may occur simultaneously, viral hepatitis agents must be considered when planning the treatment protocol.

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