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PREVALENCE OF OCCULT HEPATITIS B IN RHEUMATOLOGIC PATIENTS ON AND BEFORE STARTING IMMUNOSUPPRESSANTS

Gastroenterology

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ABSTRACT

Background Occult hepatitis B infection is characterized by negative hepatitis B surface antigen (HBsAg) and also detectable hepatitis B virus (HBV) DNA, with or without hepatitis B core antibody (anti-HBc). HBV reactivation in individuals under immunosuppressive therapy is critical as they are prone for fulminant liver failure and hepatitis flare.

Aim and Objectives The aim of this cross sectional observational study is to assess the prevalence of occult hepatitis B infection in patients having rheumatologic disorders on immunosuppressant and also in immunosuppressant naïve patients.

Materials and methods This study was done in patients admitted in Institute of Rheumatology during the time period of July 2018-December 2018. Patients having or planned to be started on biologicals,TnF alpha inhibitors , prednisolone more than 20mg for 4 weeks were evaluated. Investigations for screening for occult hepatitis B (HBsAg,TotalantiHbC) was send .HBV DNA as screening for occult infection was not due to financial constraints.

Results 50 patients were investigated in a similar manner.18 (36%) cases turned out to be Total Anti Hbc positive and HbsAg negative. One of patients on Rituximab had reactivation in form of HBsAg positivity and Total Anti HBc positivity.10 cases which were harboring occult infection were on TnF alpha blockers, 1 on Rituximab, 5 on cyclophosphamide,2 on high dose of steroid for lupus flare. Total 3 of the patients had history of blood transfusion in past. Mean age was 32-

Conclusion Prevalence of occult hepatitis B in our study population when compared with other studies (3-7%) is very high (36%). Screening for occult hepatitis B with HbsAg, Total Anti Hbc and HBV DNA should be made mandatory before starting patients on immunosuppressants.

KEYWORDS

INTRODUCTION

Rheumatologicaldiseases include diseases involving the joints,connective and soft tissue and may also affect multiple organs. More than 200 rheumatic diseases have been identified [1], many of which are known to be disorders involving immune system such as rheumatoid arthritis (RA), systemic sclerosderrma , systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS). The prevalence of rheumatoid arthritis is approximately 2% globally and about 0.43% in India[2, 3] while the prevalence of SLE usually range from 30–70/100,000 [4]. The inflammation of the affected joints may be a significant marker of ongoing activity in autoimmune and rheumatic diseases [5].

To suppress the ongoing inflammation, non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and biologic therapies can be used; nevertheless reactivation of the inflammation canbe observed among the patients with rheumatic diseases [6]. Although the exact etiology of the rheumatic diseases remains still unknown, numerous factors including genetics, environmental and several viral agents have been implicated. The presence of various viruses causing complications in rheumatic diseases has been investigated and among that hepatitis B virus (HBV) has been reported [7–9].

Hepatitis B virus is a DNA virus which belongs to the family of hepadnaviridae that infects an estimated 200–300 million people globally [10]. India is placed in locality of intermediate endemicity and the prevalence of people with chronicHBV infection has been projected to be 1.7% in the general population [11]. HBV is frequently diagnosed by serologically detecting HBsAg using enzyme-linked immunosorbent assay (ELISA) [12]. Under normal conditions, HBV remainin the hepatocytes and can be inhibited by both humoral and cellular immunity [13]. In patients having acute rheumatic diseases, the use of high risk immunosuppressive drugs may reactivate the HBV infection [14].

Although the various mechanisms involved in the inhibition of the HBV activities are far fromcompletly being elucidated, it is very clear that host factors are definitely implicated. In particular, so much evidence shows the main role played by immunological surveillance in inhibiting HBV replication and also gene expression up to the occult hepatitis B phase development [14–17]. Indeed, occult reactivation is an event usually occurring in immunocompromised patients because of the disease involving the immune system and because the therapeutic treatments also have considerably weakened the immune response.

A new form of HBV has currently emerged have been termed occult hepatitis B infection (OBI). OBI is termed as the presence of HBV DNA with undetectable HBsAg with or without HBcAb/HBsAb. Two types of OBI have been defined. One is seropositive OBI, with HBsAg negative, HBcAb/HBsAb positive and HBV DNA positivity in serum or liver tissue. The other type is seronegative OBI, which is HBsAg and HBcAb/HBsAb negative, but HBV DNA positivity in the serum or hepatic tissue [15, 16]. A recent molecular approach is being used to diagnose OBI using both nested and real-time PCR; however, the quantitative real-time PCR has been shown to have better sensitivity [17].The reactivation of OBI with significant clinical signs and symptoms of hepatitis have been reported in rheumatologic patients on treatment with immunosuppressives [18,19]

Aims and objectives

The aim of this cross sectional observational study is to assess the prevalence of occult hepatitis B infection in patients having rheumatologic disorders on immunosuppressant and also in immunosuppressant naïve patients.

Materials and methods

This study was done in patients admitted in Institute of Rheumatology during the time period of September 2018-January 2019. Patients having or planned to be started on immunosuppressant (biologicals, steroids) were evaluated with HBsAg, Total AntiHbc. If Total Anti Hbc came out as positive, HBV DNA was quantified. Total anti HBc result was rechecked everytime when it came as positive. History pertaining to Hepatitis B was taken. Statistical analysis was done using IBM SPSSS software version 20.0. Chi square test and student T test was used for analysis.

Inclusion criteria

Rheumatological patients on or before immunosupressants.

Exclusion criteria

HbsAg positive patients will be excluded from study.

Stastical analysis

Statistical analysis was done using IBM SPSSS software version 20.0. Chi square test and student T test was used for analysis.

Results

Descriptive Statistics

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	72	9	70	32.14	13.203
HBV_DNA	19	0	41100	2465.79	9383.527
Duration_treatment	72	.5	72.0	11.201	16.2534
Valid N (listwise)	19				

Mean age of the patient was 32yrs and HBV DNA was done for 19 patients. Maximum HBV DNA was 41100IU/ml.

DISEASE

DISEASE					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	SPONDYLOARTHROPATHY	25	34.7	34.7	34.7
	TAKAYASU ARTERITIS	10	13.9	13.9	48.6
	CONNECTIVE TISSUE DISEASE	37	51.4	51.4	100.0
	Total	72	100.0	100.0	

Maximum numbers of patients were having connective tissue disorders followed by spondyloarthropathy.

RISK OFTREATMENT

RISK OF TREATMENT					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	HIGH RISK	12	16.7	16.7	16.7
	MODERATE RISK	42	58.3	58.3	75.0
	LOW RISK	18	25.0	25.0	100.0
	Total	72	100.0	100.0	

High risk treatment in form of Rituximab and prednisolone 40 mg were given to 16 %. High risk treated patients are more prone for reactivation of hepatitis B.

25 (34.7%) patients had spondyloarthropathy,10 (13.9%) had Takayasu arteritis,37 (51.4%) had connective tissue disorders(SLE, SSC).High risk medications like Rituximab were given to 12(16.7%), moderate risk (TNF alpha inhibitors) to 42(58.3%),low risk (cyclophosphamide) to 18(25%) patients.19 (26.7%) patients had history of surgery in past. No association with total anti HBcpositivity (p 0.768) was found with surgery.

Antihbc					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	POSITIVE	19	26.4	26.4	26.4
	NEGATIVE	53	73.6	73.6	100.0
	Total	72	100.0	100.0	

Total Anti Hbc was positive in 19 patients and total percentage was 26.4%.

HR * antihbc Crosstabulation					
			antihbc		Total
			Positive	Negative	
HR	RITUXIMAB	Count	4	6	10
		% within HR	40.0%	60.0%	100.0%
	PREDNISOLONE 40MG	Count	0	2	2
		% within HR	.0%	100.0%	100.0%
Total		Count	4	8	12
		% within HR	33.3%	66.7%	100.0%

Total anti Hbc was positive in 33% of patients with high risk medications like Rituximab and prednisolone 40 mg.

Total anti HBC positivity	HBV DNA POSITIVITY	MAXIMUM
19	7 (36.84%)	41000COPIES/ML

Out of 19 patients with Total antiHBc positivity, 7 were having HBV DNA positivity. Maximum HBV DNA level was 41000copies/ml.

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)P VALUE	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age	Equal variances assumed	.107	.744	2.902	70	.005	9.750	3.359	3.050	16.449
	Equal variances not assumed			2.973	33.286	.005	9.750	3.279	3.080	16.420
Duration_treatment	Equal variances assumed	.826	.367	.502	70	.617	2.1931	4.3691	-6.5208	10.9071
	Equal variances not assumed			.470	28.437	.642	2.1931	4.6625	-7.3509	11.7372

As age advances, the patients are more prone to acquire total Antihbc(p value .005).

DISCUSSION

In our study, prevalence of occult hepatitis B is 26.4% in patients on and before biological. It is very high percentage when compared with other studies.

Csepregi et al. [29] in Hungry have detected a low prevalence of 4% HBsAg in 50 patients with Rheumatoid arthritis, which is not in accordance with the results of the current study. Mori [6] in Japan reported that 70/249 (25.1%) patients with rheumatoid arthritis tested positive for HBcAb but negative for HBsAg antigen. Among them, 2 (3.3%) turned out to be occult infection. Droz et al. [25] from France reported the 24/35 (68.7%) patients having rheumatic diseases had positivity for HBsAg and 31.4% for HBcAb. They found out that 2.9% of patients had occult infection. Lee et al. [30] from Taiwan studied 478 patients having rheumatic diseases undergoing treatment with anti-TNF agent who were negative for HBsAg and positive for HBcAb. They found the reactivation of hepatitis B in 8 (1.7%) patients.

Patients having rheumatic diseases and chronic HBV coinfection treated with immunosuppressives may have reactivation of the HBV infection [31]. It has been stated that HBsAg negative patients with HBcAb and/or HBsAb have achieved the resolution of HBV infection; nevertheless, among those patients, the reactivation of HBV has been increasingly reported after the immunosuppressive therapy. The reactivation of HBV infection can cause lethal hepatitis called de novo hepatitis B [32].

According to the latest evidence, it is recommended to have HBV serological screening before administering theimmunosuppressives to patients having rheumatic diseases. In addition, patients having negative HBsAg with or withoutHBcAb/HBsAb, quantitative HBV DNA testing should be done by real-time PCR in patients with resolved HBV infection [33]. Patients having rheumatic diseases are at increased risk of reactivation of hepatitis B infection compared to healthy individuals.

The increased risk can be linked with the underlying disease and associated co morbidities (diabetes, chronic obstructive pulmonary disease) and also with type of immunosuppressive therapy thatis required to control the activity of the underlying disease and the

associated organ complications. In recent studies, HBV vaccine has been administered to patients with rheumatological diseases and were reported to be safe with serologically effective. Therefore, HBV vaccination beforethe immunosuppressive treatment may serve as an alternative prophylactic for patients with rheumatic diseases.

Therapeutic regimens containing rituximab [especially combinations of rituximab with cyclophosphamide, and predniso(lo)ne] provide the maximum risk of reactivation in all HBV patients, including those with OBI [5, 21, 23] .Anti-TNF-α drugs that are commonly used in autoimmune inflammatory diseases have been reported to be associated with maximum cases of OBI reactivation.(34)

CONCLUSION

To prevent the reactivation of HBV infection, HBV serological examinations as well as HBV DNA viral load by highly sensitive molecular approaches such real-time PCR is recommended for all patients with rheumatic diseases before and during immunosuppressive therapy. Since patients with rheumatic diseases are at increased risk of acquiring HBV infection, the active HBV vaccination should be implemented for all those patients who are negative for HBsAb, HBcAb and HBV DNA. A case-control larger scale longitudinal study is recommended to confirm the present results and further elucidate the impact of medications received.

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