

Predictive Clinical Value of Rheumatoid Factor and Anti-Citrullinated Protein Antibodies as Diagnostic Tools in Cases with Non-Arthritic Chronic Hepatitis C Viral Disease

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Abstract

Background: Rheumatoid arthritis is a chronic immunological disease that causes destruction and deformity of joints. Chronic hepatitis C infection cases could develop rheumatic like clinical presenting profile. Raised rheumatoid factor in chronic HCV infection considerably reduces the diagnostic privilege of rheumatoid factor for rheumatoid arthritis coexisting with HCV infection.

Aim of the work: To determine the value of anti-citrullinated protein antibody levels in cases having chronic HCV infection in comparison to rheumatoid factor.

Methodology: The research team recruited 150 non-arthritic study subjects having chronic hepatitis C virus infection rheumatoid factor and anti-citrullinated protein antibody levels were assayed for all study subjects for statistical analysis.

Results: Rheumatoid factor +ve study subjects had statistically significantly more frequent within female gender. (p value=0.027) Rheumatoid factor high +ve cases had statistically significantly had more frequent fatty liver and higher platelets than on high RF +ve cases. (P value =0.020, <0.038 consecutively)

Conclusion: HCV cases with joint involvement were not implemented in the current research study that prevented statistical estimation of the sensitivity of anti-citrullinated protein antibody for arthritis in this cohort. Racial and ethnic differences should be put in consideration in future research studies that are recommended to be multi centric in fashion.

Introduction

Rheumatoid arthritis is a chronic form, an inflammatory systematic disease that frequently impacts hands and feet small joints. As a chronic immune disease, it could cause destruction and deformity of joints. Rheumatoid arthritis needs an effective long-term course of management [1, 2].

Clinical diagnosis establishment at an early phase of disease course of progressive development is very crucial as regards rheumatoid arthritis. On the other hand, some illnesses e.g. chronic hepatitis C virus infection can clinically present with an extrahepatic symptom and signs profile mimicking rheumatoid arthritis [3, 4].

Cases having chronic hepatitis C infection may develop rheumatic clinical presenting profile e.g., arthralgia, arthritis, vasculitis and around 19%–80% of nonarthritic hepatitis C virus chronic infected cases could have raised rheumatoid factor, the elevated prevalence of

rheumatoid factor in cases with chronic HCV infection considerably eliminates the diagnostic value of rheumatoid factor for rheumatoid arthritis in this group of cases. Anti-citrullinated protein antibody levels should be implemented in the rheumatoid arthritis cases diagnosis approach with coexisting hepatitis C virus infection, because anti-citrullinated protein antibody levels is rarely present in HCV infected cases without arthritis [5, 6]

Aim of the Work

To determine the value of anti-citrullinated protein antibody levels in cases having chronic HCV infection in comparison to rheumatoid factor

Methodology

The research team recruited 150 non-arthritic study subjects having chronic hepatitis C virus infection at the outpatient Gastroenterology and Hepatology Clinic, from April 2016 and April 2018. Inclusive

research criteria were age older than 18 years, written informed consent was obtained from all study subjects Hospital approved protocol and positivity for both anti-HCV antibody and HCV RNA was obtained. Exclusive research criteria involved known inflammatory arthritis; hepatitis B surface elevated antigen levels, past usage of antiviral therapy.

Laboratory techniques

Serum samples have been assayed for anti-HCV antibodies using a commercial kit (an immunoassay; Cobas anti-HCV II, Roche Diagnostics GmbH, Mannheim, Germany) and were verified in all study subjects by usage of HCV RNA real time polymerase chain reaction amplification (PCR; Abbott Molecular Inc, IL, U.S.A). Titer of serum Rheumatoid factor was assayed by implementing laser nephelometry for the immunoglobulin M (IgM) isotype (IMAGE Immunochemistry Systems RHF, Beckman Coulter, Brea, CA, USA) and serum levels have been considered positive at concentration levels above 20 IU/mL. anti-citrullinated protein antibody levels were assayed by usage of a commercial enzyme linked immunosorbent assay kit (EliA™ CCP, Phadia AB, Uppsala, Sweden) and an anti-citrullinated protein antibody levels below 10 U/mL have been considered within the normal range.

For rheumatoid factor and anti-citrullinated protein antibody levels, low-positive were referred to IU values that are higher than the upper limit of normal but ≤ 3 times the upper limit of normal for the laboratory and assay results; high-positive refers to IU values that are >3 times the upper limit of normal for the laboratory and assay results.

Sonographic scanning was conducted by a gastroenterologist, by usage of a Toshiba system (Aplio-300; Toshiba, Tokyo, Japan) with a 3.75-MHz convex probe to diagnose hepatic cirrhosis and fatty liver. The diagnosis of hepatic cirrhosis was conducted with a scoring system that put inconsideration four factors: hepatic surface, hepatic parenchyma, liver vessel and splenic size. Nonalcoholic fatty liver disease was categorized clinically as none, mild, moderate, or severe in accordance to the findings of hepatorenal echo contrast and hepatic brightness, deep attenuation, and vessel blurring. The current research study was approved by the Ain Shams University Hospital Ethical Committee.

Statistical methods

The collected research data were coded, tabulated, and statistically analyzed by usage of IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009. Descriptive research statistics were conducted for quantitative research data as minimum & maximum of the range as well as mean \pm SD (standard deviation) for quantitative research data, whereas it was performed for qualitative research data as number and percentage. Inferential statistical analyses were performed for quantitative research variables by usage of independent t-test in cases of two independent research groups. In qualitative research data, inferential statistical analyses for independent variables were performed by usage of Chi square test for differences between proportions and Fisher's exact test for variables with small expected numbers. The level of statistical significance was considered at P value < 0.050 is significant, otherwise is non-significant.

Results

In the current research study 150 study subjects had chronic HCV, amongst 68 (45.3%) had positive RF & 82 (54.7%) had negative RF.

Table 1: Different characteristics and the whole sample and comparison between RF positive and negative cases

Variables		Total (N=150)	RF+ve (N=68)	RF-ve (N=82)	P
Age (years)		48.4 \pm 6.7	48.6 \pm 6.7	48.2 \pm 6.7	\wedge 0.718
Sex (n.)	Male	81 (54.0%)	30 (44.1%)	51 (62.2%)	#0.027*
	Female	69 (46.0%)	38 (55.9%)	31 (37.8%)	
BMI (kg/m ²)		24.5 \pm 1.9	24.4 \pm 1.9	24.6 \pm 2.0	\wedge 0.586
Fatty liver		21 (14.0%)	8 (11.8%)	13 (15.9%)	#0.472
Liver Cirrhosis		31 (20.7%)	15 (22.1%)	16 (19.5%)	#0.701
Log HCV RNA (copies/mL)		5.4 \pm 0.9	5.5 \pm 0.9	5.4 \pm 1.0	\wedge 0.288
ALT (IU/L)		121.3 \pm 23.2	124.2 \pm 25.5	119.0 \pm 20.9	\wedge 0.173
Hemoglobin (gm/dL)		12.0 \pm 0.5	12.0 \pm 0.4	12.0 \pm 0.6	\wedge 0.810
WBC (x10 ³ /mL)		5.9 \pm 1.4	6.1 \pm 1.5	5.7 \pm 1.3	\wedge 0.077
PLT (x10 ³ /mL)		173.0 \pm 33.7	172.0 \pm 32.3	173.8 \pm 35.1	\wedge 0.739
ACPA +ve		2 (1.3%)	2 (2.9%)	0 (0.0%)	§0.204
ACPA high +ve		2 (1.3%)	2 (2.9%)	0 (0.0%)	§0.204
\wedge Independent t-test, #Chi square test, §Fisher's Exact test, *Significant					

Table 1 Reveals and displays that: rheumatoid factor +ve cases statistically significantly had more frequent female sex. (p value=0.027) other variables age, BMI, fatty liver, liver cirrhosis, log HCV RNA, ALT, hemoglobin, WBC, PLT count, Anti-citrullinated protein antibody +ve, ACPA high +ve were statistically insignificantly different between rheumatoid factor positive and negative cases (p values=0.718, 0.586, 0.472, 0.701, 0.288, 0.173, 0.810, 0.077, 0.739, 0.204, 0.204, consecutively).

Table 2: Comparison between RF high positive and non-high positive cases

Variables		High RF+ (N=13)	Non High RF+ (N=137)	P
Age (years)		45.9 \pm 7.0	48.6 \pm 6.6	\wedge 0.164
Sex (n.)	Male	6 (46.2%)	75 (54.7%)	#0.553
	Female	7 (53.8%)	62 (45.3%)	
BMI (kg/m ²)		25.4 \pm 2.3	24.4 \pm 1.9	\wedge 0.071
Fatty liver		5 (38.5%)	16 (11.7%)	§0.020*
Liver Cirrhosis		2 (15.4%)	29 (21.2%)	§1.000
Log HCV RNA (copies/mL)		5.8 \pm 1.1	5.4 \pm 0.9	\wedge 0.203
ALT (IU/L)		130.5 \pm 24.1	120.5 \pm 23.0	\wedge 0.138
Hemoglobin (gm/dL)		12.0 \pm 0.5	12.0 \pm 0.5	\wedge 0.992
WBC (x10 ³ /mL)		6.4 \pm 1.9	5.9 \pm 1.3	\wedge 0.236
PLT (x10 ³ /mL)		191.5 \pm 26.7	171.2 \pm 33.9	\wedge 0.038*
ACPA +ve		1 (7.7%)	1 (0.7%)	§0.166
ACPA high +ve		1 (7.7%)	1 (0.7%)	§0.166
\wedge Independent t-test, #Chi square test, §Fisher's Exact test, *Significant				

Table 2 shows that: shows that: RF high +ve cases had statistically significantly had more frequent fatty liver and higher platelets than on high RF +ve cases. (p value =0.020, <0.038 consecutively) whereas other variables age, gender, BMI, liver cirrhosis, log HCV RNA, ALT, hemoglobin, WBC, platelet count, ACPA +ve, ACPA high +ve were statistically insignificant (p values =0.164, 0.553, 0.071, 1.00, 0.203, 0.138, 0.992, 0.236, 0.166, 0.166, consecutively)

Discussion

The current research study findings revealed the following results in which comparative statistical analysis between rheumatoid factor positive and negative study subjects have revealed that rheumatoid factor +ve cases statistically significantly had more frequent female sex (P value=0.027). Comparative statistical analysis between rheumatoid factor high positive and non-high positive cases have revealed that: RF high +ve cases had statistically significantly had more frequent fatty liver and higher platelets than on high RF +ve cases. (P value =0.020, <0.038 consecutively) HCV chronic infection clinically presents with various extrahepatic signs and symptoms including arthritis. In various clinical scenarios of HCV chronic infection, joint symptoms could appear similar to the beginning of rheumatoid arthritis symptom profile [7, 8].

A previous research study involved a large cohort of cases of around 271 study subjects having double- positive anti-HCV antibody and HCV RNA. The prevalence rates of positive rheumatoid factor and ACPA have been 47.2% and 1.1%, consecutively. Interestingly in addition to current harmony to the research study performed by our research team prevalence of positive rheumatoid factor was nearly alike to that revealed and displayed in prior research studies [9, 10].

The high rate of rheumatoid factor sero-positivity in cases having HCV chronic infection clinically presents a challenge in diagnosis. Furthermore, a previous nationwide population-based research study denoted that HCV chronic form of infection is correlated with rheumatoid arthritis clinical and pathological course of development. Consequently, the existence of rheumatoid factor is of minute clinical value in discrimination between rheumatoid arthritis and coexisting HCV-related arthritis, particularly due to a high-positive rheumatoid factor serum level [11].

Moreover, the prevalence of anti-citrullinated protein antibody levels in a prior research study similar in methodology to the current research was around 1.1%, that have shown great similarity in addition to prior research studies in HCV cases. According to previous research studies, anti-citrullinated protein antibodies are easily observed in cases having chronic form of HCV infectious disease with coexisting joint involvement on the other hand not in HCV-infected cases not having joint involvement [1, 4].

Anti-citrullinated protein antibody levels were priority observed by various research teams to be existing with high statistical specificity in the bulk of cases having rheumatoid arthritis, but only rarely existing in the serum of cases with other clinical diagnosis. Additionally, previous research teams revealed and displayed that the calculated statistical prevalence of high-positive anti-citrullinated protein antibody levels was correspondingly low at 1.1%. As a result, anti-citrullinated protein antibody could ensure enhanced clinical significance in implementation in clinical diagnosis of rheumatoid arthritis in the current and previously similar research studies [2, 6]

In great harmony with the current research study results a prior research has shown that female study subjects revealed a greater prevalence of positive rheumatoid factor. This could be justified in correlation to gender-sex hormonal serum levels that could trigger autoantibodies production [3, 7].

A prior research team investigated a large, single-center cohort of 1202 study subjects having HCV chronic infection and mentioned that female gender, rising age, and widespread hepatic fibrosis are clinical risk factors for the existence and emergence of extrahepatic symptom profile. Age have not been statistically variable between HCV-infected Cases with or without rheumatoid factor in a research study previously conducted having a similar approach to the current research however other research groups mentioned that 10%-25% of cases aged above 70 years have a positive rheumatoid factor test result [4, 8].

Furthermore, the HCV viral load did not vary in the current research study between rheumatoid factor -positive/negative Research groups. In harmony with this finding Ramos et al, research team revealed no statistical difference in rheumatoid factor activity levels between those with dissimilar serum levels HCV RNA. Besides, it was mentioned by a group of investigators priory a reduced rheumatoid factor titer in non-responders administered combination therapy with PEG-INF alpha-2b and ribavirin. It was justified by the fact that INF besides ribavirin antagonizes the inflated immunological responsiveness; Apart from viral outcome i.e. Rheumatoid factor titer was not correlated to viral load in cases having HCV infection [5, 9].

A prior research study revealed and displayed that from 23 cases having Nonalcoholic fatty liver disease and revealed a frequency of positive rheumatoid factor of 13%. The pathological course of development of Nonalcoholic fatty liver disease is not completely understood; on the other hand, it was revealed previously that tumor necrosis factor-alpha, interleukin 8, and 6 concentrations levels are statistically significantly raised in cases with biopsy diagnosed nonalcoholic steatohepatitis. These research results and findings denote that inflammatory cytokines are correlated with the pathological development and/or progression of fatty liver disease. Additionally, cytokines could additionally trigger B cells to yield antibodies [7, 11].

Conclusions

Some restriction in the current research study exists since the research teams haven't enrolled rheumatoid arthritis cases patients or a healthy study subject that makes it determine variabilities in serum markers statistical prevalence of serum markers. Furthermore, HCV cases with joint involvement were not implemented in the current research study that prevented statistical estimation of the sensitivity of anti-citrullinated protein antibody for arthritis in this cohort. Finally racial and ethnic differences should be put in consideration in future research studies that are recommended to be multi centric in fashion.

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