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The value of anti-rods and rings antibodies in patients with nonhepatitis virus infection
A single-center retrospective study from Southwest China

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Abstract

The aim of this study was to retrospectively investigate the clinical significance of anti-rods and rings (anti-RR) antibodies in nonhepatitis virus infection patients from Southwest China.

Anti-RR antibodies were determined by indirect immunofluorescence assay in a group of 19,935 individuals with antinuclear antibodies test from January 2017 to December 2019. The laboratory and clinical data were collected. Finally, 66 samples with anti-RR antibodies (0.33%) were detected.

In Wilcoxon rank sum test, gamma glutamyl transferase ($Z = -3.364$, $P = .001$), alpha-l-fucosidase (AFU) ($Z = -2.312$, $P = .021$), uric acid ($Z = -1.634$, $P = .047$) and red blood cell distribution width ($Z = -2.285$, $P = .022$) were higher in metabolic disease group than nonmetabolic disease group. In independent-samples t test, endogenous creatinine clearance was higher in metabolic disease group than nonmetabolic disease group ($t = 2.061$, $P = .045$). During the follow-up period of 37 patients with anti-RR antibodies for 1 to 60 months, the titers of anti-RR were significantly increased in the metabolic disease group ($Z = -2.346$, $P = .019$). In binary logistic regression analysis, triglycerides (odds ratio 3.679, 95% confidence interval 1.467–24.779, $P = .048$) was associated with elevated titers of anti-RR antibodies.

In summary, anti-RR in non-hepatitis patients may be a manifestation of metabolic disorders, and has a certain correlation with routine laboratory indicators, which is worthy of the attention from clinicians.

Abbreviations: γ-GGT = gamma glutamyl transferase, AFU = alpha-l-fucosidase, ANAs = antinuclear antibodies, Anti-RR = anti-rods and rings, Ccr = endogenous creatinine clearance, CTPS1 = cytidine triphosphate synthase 1, HCV = hepatitis C virus, Ig = immunoglobulin, IMPDH2 = inosine monophosphate dehydrogenase 2, RDW-SD = standard deviation of red blood cell volume distribution width, SD = mean ± standard deviation.

Keywords: antinuclear antibodies titer, anti-rods and rings antibodies, metabolic disease

1. Introduction

As characteristic markers of autoimmune diseases, antinuclear antibodies (ANAs) play an important role in the clinical diagnosis and condition detection. Previous studies have shown that autoantibodies can also be found in infectious diseases, cancer and even healthy people.[1–3] Therefore, long-term and large-scale clinical studies on the clinical significance of different types of autoantibodies were required. As characteristic fluorescence patterns in the detection of ANAs by indirect immunofluorescence assay, anti-rods and rings (anti-RR) antibodies were first

reported in the serum of a patient with hepatitis C virus (HCV) infection receiving ribavirin.[4] After that, anti-RR antibodies were reported in the serum of a Chinese female patient with systemic lupus erythematosus. She received antiviral drugs and immunosuppressant therapy.[5] Since then, a rare case of high-titer anti-RR antibodies in primary biliary cholangitis had been reported.[6] It was reported that anti-RR antibodies were mainly found in HCV patients treated with interferon-α/ribavirin (IFN-α/RBV) combination therapy.[7–9]

Early studies revealed that 2 key enzymes in the nucleotide synthetic pathway such as cytidine triphosphate synthase 1 (CTPS1) and inosine monophosphate dehydrogenase 2 (IMPDH2) were highly enriched in anti-RR antibodies.[4,10] But 2 years later, more research showed that IMPDH2 was indeed the main target of anti-RR while CTPS1 was an unlikely 1.[11–13] It was reported that IMPDH2 could catalyze the conversion of inosine monophosphate into xanthosine monophosphate in the GTP biosynthesis pathway and CTPS1 could catalyze the conversion of uridine triphosphate into cytidine triphosphate.[14] Two independent cohorts study showed that anti-RR antibodies and anti-IMPDH2 response to HCV patients with interferon-α/ribavirin (IFN/R) therapy were significant heterogeneity. It also affirmed that anti-RR and anti-IMPDH2 had a negative correlation with HCV patients to the overall effect of IFN/R treatment response.[15] Another study showed that HeLa cells cultured without glutamine could form short rods (<2 μm) after 24 hours, and longer rods (>5 μm) after 48 hours. It is worth noting that these RR structures disassembled in a short time after supplementation with glutamine or guanosine.[16] The above research suggested that the RR structures might be an adaptive metabolic response related to the breakdown of glutamine homeostasis. Studies have shown that the metabolism of glutamine in key organs, such as the gut and liver, is also important to cells of the immune system.[17–19]

The detection of anti-RR antibodies and clinical laboratory characteristics in nonhepatitis virus infected population were rarely reported. Considering the key point of anti-RR in nucleic acid and phospholipid biosynthesis, we compared the clinical data between anti-RR patients without hepatitis infection and healthy controls previously (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A168). We found that the serum lipids, glucose and uric acid of patients with anti-RR were significantly higher than those of healthy controls (Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A169). Combined with the clinical diagnosis and the follow-up of some patients, we assumed that anti-RR antibodies might be related to the metabolic disorders of the nonhepatitis infected patients.

In this study, anti-RR antibodies and clinical data were collected from patients in Peoples Hospital of Deyang City from January 2017 to December 2019. The data were retrospectively analyzed to understand the association between anti-RR in nonhepatitis virus infected patients and laboratory indicators of metabolic disorders. We also analyzed risk factors that influence the titer of anti-RR antibodies during the follow-up period.

2. Materials and methods

2.1. Study design and population

We performed a retrospective study on 19,935 patients from Peoples Hospital of Deyang City from January 2017 to December 2019. A total of 98 patients who had anti-RR antibodies were selected. All patients were tested for biomarkers of hepatitis virus, including: hepatitis A virus immunoglobulin M (IgM), hepatitis B virus surface antigen, hepatitis B e antigen, HBV deoxyribonucleic acid, HCV antibody, HCV ribonucleic acid and hepatitis E virus IgM.

Metabolic syndrome was diagnosed according to the definition and diagnostic criteria by the international diabetes federation in 2005.[20] The criteria indicated that the presence of 3 or more can be diagnosed. Patients were diagnosed by epidemiologists and without complete data were excluded. Finally, 66 patients were included. This study was approved by the Ethics Committee of Peoples Hospital of Deyang City (Registration number: ChiCTR2000032468). This study complied with the declaration of Helsinki and was approved by the Ethics Committee of Peoples Hospital of Deyang City and an informed consent for using their clinical characteristics and laboratory data was obtained from all cases enrolled.

2.2. Methods

Serum samples were tested for ANA by indirect immunofluorescence assay coated with HEp-2 cells (EUROIMMUN, GERMANY). Anti-RR antibodies were observed by fluorescence microscope (OLYMPUS BX51). A 100W ultra-high pressure mercury lamp (U-LH100HG) was used as the light source and the intensity of the light source was corrected. The excitation filter, the splitting filter and the blocking filter were 488 nm, 510 nm and 520 nm respectively. The hepatitis virus markers were detected by electrochemical luminescence with Roche MODULAR ANALYTICS E170. The clinical indexes of biochemistry, immunology, and hematology were the routine clinical examinations.

2.3. Clinical data

Demographic and clinical data were collected from the medical records. Follow-up information included ANAs initial titer, follow-up time, clinical diagnosis, immunosuppressants and antibiotics. Laboratory tests of liver function included the following items: total bilirubin, direct bilirubin, total protein, globulin, aspartate transaminase, alanine aminotransferase, prealbumin, gamma glutamyl transferase (γ-GGT), alkaline phosphatase, cholinesterase, 5'-nucleotidase and alpha-l-fucosidase (AFU). Laboratory tests of renal function included the following items: glucose, urea, creatinine, uric acid, cystatin C, endogenous creatinine clearance (Ccr) and β2 microglobulin. Laboratory tests of immunocorrelation included IgG, IgA, IgM, complement 3 and complement 4. Laboratory tests of blood cell analysis included the following items: white blood cell, red blood cell, hemoglobin, standard deviation of red blood cell volume distribution width (RDW-SD [standard deviation]), coefficient of variation of red blood cell distribution width, platelet, mean platelet volume, platelet-large cell ratio, platelet distribution width, and plateletocrit.

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 22.0). Normally distributed data were presented as mean ± SD, nonnormal variables were expressed as median interquartile range.

Categorical variables were presented as percentage and frequency. Comparison between groups was evaluated with independent-samples t test with normal distribution and Wilcoxon rank sum test with non-normal distribution. Although $P < .05$ was used to define statistical significance for all inferential statistics, a $P \leq .15$ was used in univariate analysis for inclusion of putative risk factors into the multivariate (adjusted) model. A $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of the population

The demographics and clinical characteristics of all the anti-RR individuals grouped by metabolic diseases were illustrated in Table 1.

In this analysis, age (54.0 vs 57.5, $P = .174$) and gender (41% vs 22%, $P = .188$) showed no significant difference between the 2 groups. There was no significant difference in the geometric mean of anti-RR titers (227 vs 150, $P = .161$). The median of triglycerides (1.37 vs 1.10, $P = .044$) was higher in metabolic disease group than it in nonmetabolic disease group. There was no significant difference between the different groups in body mass index, blood pressure, glucose, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol ($P > .05$).

3.2. Comparison between laboratory data in metabolic disease group and nonmetabolic disease group

Comparisons of laboratory data between different groups were illustrated in Table 2. In metabolic disease group, γ-GGT (40.0 vs 16.0, $P = .001$), AFU (24.0 vs 18.0, $P = .021$), uric acid (355.8 vs 302.2, $P = .047$), and RDW-SD (45.2 vs 43.8, $P = .022$) were higher than nonmetabolic disease group. While in metabolic disease group, Ccr (75.2 vs 91.1, $P = .045$) was lower than nonmetabolic disease group. Other data showed no difference between the different groups ($P > .05$).

3.3. The follow-up titers of the anti-RR antibodies

The follow-up of the anti-RR antibodies in metabolic disease group and in nonmetabolic disease group was illustrated in Table 3.

In metabolic disease group, the proportion of male was higher (52.63%) in the metabolic disease group and lower (16.67) in the non-metabolic disease group ($\chi^2 = 5.246$, $P = .022$). There were no significant differences in age, follow-up time, initial titer, and follow-up titer between the 2 groups ($P > .05$). However, the titers of anti-RR were significantly increased in the metabolic disease group ($Z = -2.346$, $P = .019$). In metabolic disease group, the titers of 19 (100%) patients increased (Table S3, Supplemental Digital Content, http://links.lww.com/MD2/A170). In non-metabolic disease group, the titers of 14 (77.8%) patients increased, 3 (16.7%) patients did not show obvious change and 1 (5.6%) patient decreased (Table S4, Supplemental Digital Content, http://links.lww.com/MD2/A171). Follow-up results showed that the patient with decreased titer received antituberculosis treatment for 5 months. Other 3 patients (1 case of tuberculous pleurisy, 1 case of insomnia and 1 case of depressive episode) had no significant change in titers after 5 months of antituberculosis therapy, 13 months treatment for osteoarthritis and 6 months of psychotropic drug treatment, respectively.

3.4. Binary logistic regression analysis predictors of elevated titers of anti-RR antibodies

We constructed the binary logistic regression analyses to identify the predictors of elevated titers of anti-RR antibodies in the follow-up. As presented in Table 4, triglycerides (odds ratio 3.679, 95% confidence interval 1.467–24.779, $P = .048$) had a significant effect on the increase of titers, while other laboratory data had no statistical difference on the titers ($P > .05$).

4. Discussion

Anti-RR antibodies are rare fluorescence patterns in the ANAs. This study showed a low frequency (0.49%) of anti-RR antibodies in the ANAs. In a similar study, Zhang et al studied the same fluorescence patterns and reported the frequency (0.10%) in Han Chinese population.[1] Similarly, Climent et al reported that 87 patients from 20,000 serum samples had the anti-RR patterns during a 4-year retrospective study.[21] However, the frequency of anti-RR antibodies was higher in chronic HCV infection patients and tissue samples than in the general population. Keppeke et al reported a high frequency (91.0%) in 45 acral lentiginous melanoma paraffin-embedded

Table 1			
Demographic characteristics of the studied individuals.			
Characteristics	**Metabolic disease median (IQR/SD)**	**Nonmetabolic disease median (IQR/SD)**	**_P_ value**
Gender n (%)			
Male	16 ± 4.1	6 ± 2.2	.188
Female	23 ± 5.9	21 ± 7.8	
Age (yr)	54.0 (47.5–67.0)	57.5 (42.2–65.0)	.174
Anti-RR titer	227 (100–320)	150 (100–320)	.261
BMI (kg/m^2)	25.6 (18.1–30.8)	24.9 (19.4–30.1)	.226
Blood pressure (mm Hg)			
Systolic	128 (115–137)	130 (106–144)	.365
Diastolic	80 (71–87)	80 (77–91)	.973
Glucose	6.05 (4.77–7.33)	5.73 (5.04–6.95)	.057
Total cholesterol	4.20 (3.28–5.20)	4.91 (3.31–5.39)	.073
HDL-C	1.21 (0.84–1.57)	1.75 (1.07–2.12)	.079
LDL-C	2.26 (1.84–3.21)	2.57 (1.41–3.78)	.068
Triglycerides	1.37 (0.82–1.77)	1.10 (0.73–1.61)	.044

Anti-RR = anti-rods and rings, BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol.

Table 2

Clinical laboratory data of different groups.

Laboratory data	Metabolic disease median (IQR/ SD)	Non-metabolic disease median (IQR/ SD)	Z/t	P value
Liver function				
Total bilirubin	9.9 (6.8–13.9)	12.4 (6.9–19.0)	−0.798	.425
Direct bilirubin	3.7 (2.2–5.4)	4.3 (2.1–6.5)	−0.028	.978
Total protein	68.0 (62.6–75.5)	66.4 (62.7–74.3)	−0.574	.566
Globulin	26.4 (23.1–31.8)	26.0 (20.3–30.0)	−1.085	.278
Aspartate transaminase	29.0 (22.0–40.0)	23.0 (18.5–36.5)	−1.508	.131
Alanine aminotransferase	28.0 (15.0–51.0)	19.0 (11.5–37.5)	−1.517	.129
γ-glutamyl transferase	40.0 (19.4–93.5)	16.0 (11.5–33.5)	−3.364	.001
Alkaline phosphatase	76.0 (60.0–101.0)	65.0 (51.0–87.5)	−1.443	.149
5'-nucleotidase	5.0 (3.0–7.0)	5.0 (3.5–6.0)	−0.254	.799
Alpha-I-fucosidase	24.0 (20.5–29.5)	18.0 (16.0–24.5)	−0.412	.021
Cholinesterase	6066.5 ± 2425.9	6938.6 ± 2570.6	1.804	.285
Prealbumin	214.1 ± 84.3	209.4 ± 62.2	−0.193	.848
Renal function				
Ccr	75.2 ± 26.5	91.1 ± 24.4	2.061	.045
Urea	5.9 (4.0–6.8)	5.8 (4.5–6.1)	−0.419	.675
Creatinine	62.5 (57.3–98.8)	57.0 (51.5–69.2)	−1.350	.177
Uric acid	355.8 (255.3–527.0)	302.2 (264.0–332.5)	−1.634	.047
Cystatin C	1.1 (0.8–1.6)	0.9 (0.7–1.1)	−1.552	.121
β2 microglobulin	2.5 (1.9–4.7)	1.9 (1.8–2.6)	−1.700	.089
Serum immune parameters				
Ig G	15.4 ± 11.8	12.9 ± 2.7	−0.800	.429
Ig A	2.3 ± 0.9	2.3 ± 1.0	0.017	.986
Ig M	1.3 (0.7–3.1)	1.2 (0.8–1.8)	−1.596	.111
Complement 3	1.1 ± 0.3	1.1 ± 0.4	−0.093	.927
Complement 4	0.3 (0.2–0.5)	0.3 (0.3–0.4)	−0.096	.924
Blood cell analysis characteristics				
White blood cell	7.3 ± 3.5	6.2 ± 3.0	−0.979	.334
Red blood cell	3.8 ± 0.8	4.3 ± 0.5	1.795	.081
Hemoglobin	116.2 ± 27.2	112.0 ± 33.7	0.414	.681
RDW-CV	13.2 (12.8–15.5)	12.9 (12.4–14.0)	−1.205	.233
RDW-SD	45.2 (43.3–52.9)	43.8 (43.0–44.8)	−2.285	.022
Platelet	167 (108–265)	179 (152–263)	−1.231	.222
Mean platelet volume	11.9 ± 1.9	12.2 ± 1.7	−0.453	.654
Platelet-large cell ratio	40.3 ± 14.1	41.4 ± 13.2	−0.203	.841
Platelet distribution width	16.3 ± 4.0	16.5 ± 4.8	−0.099	.922
Plateletocrit	0.18 (0.15–0.34)	0.22 (0.18–0.35)	−0.913	.370

Ccr = endogenous creatinine clearance, Ig = immunoglobulin, RDW-CV = coefficient of variation of red blood cell distribution width, RDW-SD = standard deviation of red blood cell volume distribution width.

tissue samples and a frequency (39.0%) in 59 melanocytic nevi samples.[2] In line with these data, Covini et al reported that anti-RR structures had been detected in 15 out of 75 (20%) chronic HCV infection patients.[22] Stinton et al reported a frequency (4.8%) in 315 chronic HCV infection patients.[23] Considering the high prevalence of anti-RR antibodies in patients with chronic HCV infection, we excluded 32 patients with HBV or HCV in this study.

In August 2014, the international consensus on antinuclear antibody pattern meeting made clear that anti-RR was categorized as a required pattern in cytoplasmic pattern.[24] As mentioned above, the majority studies on anti-RR antibodies still focused on the efficacy of IFN/R therapy in HCV patients. However, we often encountered non-HCV infected patients with anti-RR antibodies in clinical. How to explain the clinical significance of anti-RR in these patients is the main purpose of

Table 3

Changes in titers of anti-RR antibodies between different groups.

Characteristics	Metabolic disease median (IQR/SD)	Non-metabolic disease median (IQR/SD)	Z/t	P
Number	19	18	–	–
Gender male, n (%)	10 (52.63)	3 (16.67)	5.246	.022
Age (yr)	58.79 ± 19.91	49.61 ± 17.82	1.475	.149
Follow-up (mo)	21.95 ± 11.30	31.50 ± 20.63	−1.759	.087
Initial titer	37.89 (0.00, 100.00)	64.44 (0.00, 100.00)	−0.293	.770
Follow-up titer	380.00 (100.00, 320.00)	173.33 (100.00, 320.00)	−0.749	.454
Changes in titers	342.10 (100.00, 320.00)	108.89 (0.00, 100.00)	−2.346	.019

IQR = interquartile range, SD = standard deviation.

Table 4

Binary logistic regression analysis to assess predictors of elevated titers of anti-RR antibodies.

Characteristics	β	Wald	P	OR	95%CI
Glucose	−0.032	0.054	.816	0.968	0.737–1.272
Total cholesterol	0.066	0.026	.872	1.068	0.481–2.376
HDL-C	−3.841	2.192	.139	0.021	0.801–3.467
LDL-C	1.291	1.759	.085	1.637	0.540–2.518
Triglycerides	3.517	4.839	.048	3.679	1.467–24.779
Aspartate transaminase	0.011	0.944	.331	1.011	0.989–1.034
Alanine aminotransferase	−0.010	0.841	.359	0.990	0.968–1.012
γ-glutamyl transferase	−0.007	1.038	.308	0.993	0.993–1.017
Alkaline phosphatase	0.017	3.020	.082	1.017	0.998–1.036
Alpha-l-fucosidase	−0.025	0.436	.509	0.975	0.904–1.051
Ccr	0.042	3.590	.058	1.043	0.999–1.088
Uric acid	0.002	0.315	.575	1.002	0.996–1.007
Cystatin C	0.021	0.230	.631	1.021	0.938–1.112
β2- microglobulin	0.325	2.866	.090	1.384	0.950–2.017
Immunoglobin M	−0.560	1.375	.241	0.571	0.224–1.456
Red blood cell	−0.025	0.001	.970	0.976	0.268–3.553
RDW-SD	0.102	1.953	.162	1.107	0.960–1.277

Ccr = endogenous creatinine clearance, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, RDW-SD = standard deviation of red blood cell volume distribution width.

our study. In this study, the laboratory results showed that γ-GGT, AFU, Ccr, uric acid, and RDW-SD in the metabolic disease group were significantly different from the control group in nonhepatitis patients. Meanwhile, triglycerides were significantly different in the comparison of the basic characteristics of the metabolites and the nonmetabolites. We assumed that anti-RR antibodies might be a manifestation of adaptive response, which was associated with metabolic disorders in nonhepatitis infected patients. In agreement with our data, Arasteh et al reported that the level of γ-GGT was enhanced progressively with increasing the obstruction severity of arteries.[25] Similarly, Ndrepepa et al reported an association between elevated γ-GGT activity level and a risk of incident coronary heart disease or coronary heart disease -related mortality.[26] In addition, Bailey CJ reported that the lowering of uric acid by sodium/glucose co-transporter-2 inhibition may assist in reducing adverse cardiovascular events and slowing progression of chronic kidney disease in type 2 diabetes.[27]

However, reports on diseases related to AFU mainly focus on cardiovascular diseases, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma.[28–30] It was worth noting that all of the 5 biomarkers with significant differences were within the normal reference range. Patients usually ignored this due to insufficient understanding of autoantibodies. As we had shown in this study, there were no significant difference in autoimmune markers, which might affect clinician's judgment. During the follow-up period of 37 patients for 1 to 60 months, the titers of all patients with metabolic disease increased. Two of them died shortly after a titer greater than 1:1000 occurred. Binary logistic regression analyses showed that triglycerides had a positive effect on the increase titers of anti-RR. Previous studies have shown that patients with elevated triglyceride levels were at increased risk for ischemic events.[31] Actually, both intracellular accumulation of nonesterified fatty acids and triglycerides promoted endoplasmic reticulum stress, mitochondrial uncoupling, oxidative stress, and altered membrane composition/function, finally promoting inflammatory response and cell death.[32] This is significantly different from the expression of anti-RR in HCV infection patients treated with pegylated interferon (PI) and ribavirin (RBV). The titer of anti-RR decreased significantly after discontinuation of PI-RBV treatment,[33] but continued to increase in metabolic disease. Obviously, anti-RR antibodies were not only appeared in HCV patients but also arisen in patients with metabolic diseases. In particular, we found that the number of anti-RR antibodies in nonhepatitis infected patients was higher than that of hepatitis infected patients, which is worthy of attention from clinicians.

We recognize the relatively small sample of number of individuals as a main limitation of this study. At the same time, we noted that the P value of triglycerides in the binary logistic regression analyses was close to .05. In spite of this limitation, our study contributes with a new argument in which the anti-RR antibodies may be a correlation with metabolic diseases, and has a certain correlation with routine laboratory indicators. Therefore, the clinical significance of anti-RR in nonhepatitis infected patients remains to be further studied.

5. Conclusions

In summary, the utility of this study is to clarify the association between anti-RR and laboratory indicators of metabolic disorders. The appearance of anti-RR in nonhepatitis patients may be a manifestation of metabolic disorders, and has a certain correlation with routine laboratory indicators, which is worthy of attention from clinicians.

Author contributions

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