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Study of the relation of Anti-Ro and Anti-La Antibodies with cardiac arrhythmia and other ECG abnormalities in Systemic Lupus Erythematosus

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Abstract

Introduction: Arrhythmias and conductive system disorders are among the cardiovascular aggravations brought about by Systemic lupus erythematosus. Anti-Ro/SSA and LA antibodies are often recognized in connective tissue disease patients as well as in apparently healthy people.

Aim of the work: Assess the role of Anti-Ro and Anti-La antibodies as hazard factors for arrhythmia in grown-up SLE patients.

Patients and Methods: Cross_ sectional clinical investigation. A sum of 70 SLE cases going to the outpatient and inpatient divisions of rheumatology, Sohag University Hospitals; remembered for investigations. All members will be exposed to the accompanying: Full history, General and local assessment, Routine examinations: complete blood picture, erythrocyte sedimentation rate, liver capacities, kidney capacities, ANA IF, Anti Ro and Anti La appraisal by Immunoblot measure and Electrocardiogram

Results: 13 (41.9%) of our patients who had positive anti_ RO and LA had strange ECG findings, while 18 (58.1%) of them had typical ECG, just oral/nasal ulcers and Anti-RO/LA were an independent risk factor for abnormal ECG. Disease duration was nonsignificant and positive corresponded with disease activity by SLEDAI score

Conclusion: This study exhibited that the grown-up heart may represent a goal for the anti-Ro⁄SSA antibodies 'arrhythmogenicity. Notwithstanding, the particular rhythm changes happened to appear to be, correlated with age, as shown by the way that while ventricular repolarization variations from the norm (specifically QTc prolongation) are the transcendent finding in the adults, the inclusion of conduction system is limited to the fetal heart only.

Keywords: SLE, Anti-Ro, and Anti-La, Arrhythmias.

Introduction

The systemic lupus erythematosus (SLE), is an autoimmune disease in which the immune system of the body attacks self- tissues in many organs and systems of the body. Common manifestations include unexplained fever, joint involvement (arthralgia and/or arthritis), chest pain, hair falling, mouth ulcers, swollen lymph nodes, feeling tired, and a red rash which is more frequent on the face. Regularly there are times of sickness, called flares, and times of remission in which there are scarcely any manifestations (1).

Arrhythmias and conductive system disorders are between the cardiovascular unsettling influences brought about by (SLE). Immuno-mediated harm, atherosclerotic complications, or even the antagonistic impact of the treatment appear to be the components included regularly in the pathophysiology of those disturbances (1).

The literature has not given appropriate clinical regard for the advancement of arrhythmias in those patients (2). Electrocardiography (ECG) is a reasonnable, generally accessible noninvasive instrument that can identify the significant system (SLE)– related cardiovascular inclusion, including rhythm disturbances and ventricular repolarization variations from the norm. Irregularities recognized on (ECG) at rest that might be related to an expa=-nded risk for cardiovascular (CV) disturbances incorporate ST-section variations from the norm, T-wave anomalies, left ventricular hypertrophy (LVH), left-axis deviation, and bundle branch block (3).

The subsequent mortality top in SLE could be identified with the advanceement of arrhythmias, particularly because of the sudden death(3).

Anti-Ro/SSA antibodies, solely having a place with the IgG class, comprise of 2 subtypes-(i.e., anti_ Ro/SSA-60 kD and anti-Ro/SSA-52 kD) and are as often as possible identified both in patients with connective tissue disease (CTD) and healthy persons (4).

The pathogenic role of the anti_Ro and anti _la antibodies on the imamture heart conductive system is all around perceived, extensive proof connect the transplacental passage of anti_ Ro/SSA from the mother to the baby with the danger of creating the congenital atrioventricular block (5).

Aim of the work:

This study aims to assess the role of Anti-Ro and Anti-La antibodies as risk factors for arrhythmia in adult SLE patients

Patients and Methods:

Design: Cross_ sectional clinical study.

Patients: A total of 70 SLE cases attending the outpatient clinic and inpatient departments of rheumatology, Sohag University Hospitals; included in the study.

Methods:

All of the participants subject to the following:

Full history

Demographic data

- Age
- Sex
- Marital status
- Occupation
- personal history
- A detailed history of general health conditions and chronic or current diseases.
- History of all possible SLE manifestations and complications.

General and local examination including:

- Vital signs and general look
- Full musculoskeletal examination.
- Full mucocutaneous examination.
- Complete rheumatological examination.
- Ophthalmological examination
- Dermatological examination
- Neurological examination.
- Examination of other body systems and organs.
- SLE activity index **SLEDAI** ***(Romero-Diaz et al, 2011)***

Investigations:

Routine investigations

- complete blood picture
- erythrocyte sedimentation rate
- liver functions
- kidney functions

ANA IF:

By immunofluorescence technique:

Anti Ro and Anti La assessment by Immunoblot assay:

Antibodies are utilized to recognize target proteins on the western smudge (immunoblot). The antibodies are conjugated with fluorescent or names or catalysts that give resulting reaction

with an applied reagent, prompting shading or discharge of light

Electrocardiogram (ECG).

It is a non-invasive demonstrative test that assesses the heart's electrical system to survey for heart illness and improves comprehension of pulse, rhythm, and some types of structural heart diseases and evaluates heart efficiency. It utilizes flat metal cathodes set on the chest to recognize the electrical charges created by the heart as it pulsates, which are then diagramed

Statistical analysis:

Statistical package for social sciences (IBM-SPSS), version 24 IBM- Chicago, USA (May 2016) was used for statistical data analysis.

Data articulated as mean, standard deviation (SD), percentage, and number. Mean and the standard deviation was used as a descriptive value for quantitative data, whereas the percentage and number were used to explain qualitative data.

A student t_ test was used to compare the means between the two groups.

Pearson Chi _square was used to compare percentages of qualitative data, and Fisher's Exact Test was used for nonparametric data.

Pearson correlation test was used to compare two quantitative variables. The value of (r) is explained as being negligible if <0.2, weak if between 0.2-0.4, moderate if between 0.4-0.7 and strong if >0.7. Positive (r) means direct correlation, while a negative (r) means inverse correlation.

for every one of these tests, the level of significance (P-value) can be explained as:

No significance $P > 0.05$
Significance $P < 0.05$
High significance $P < 0.001$.

Inclusion criteria

Patients diagnosed as SLE according to SLICC 2012 or ACE/EULAR 2017 classification criteria.

Age above 18 years old.

Exclusion criteria:

Patients with simultaneous systemic diseases such as coronary artery disease, malignancy, thyroid function disorder.

Other autoimmune diseases including rheumatoid arthritis, scleroderma, mixed connective tissue disease, and polymyositis.

History of smoking.

Diabetes mellitus.

Results

Our study included 70 SLE patients, we found that 23 (32.9%) had abnormal ECG findings, and 47 (67.1%) had normal ECG. We found that 12 (17.1%) of our patients had ischemia, 9 (12.9%) had sinus tachycardia, and only 1 patient (1.4%) had left bundle branch block (arrhythmia). There was a nonsignificant difference between ECG findings regarding age, disease duration, SLEDAI score, and Anti RO and LA.

In this study, we found that mean age of patients had abnormal ECG was older than normal ECG patients with significant difference (p=0.04), also mean duration of disease was longer in patients had abnormal ECG than normal ECG patients with significant difference (p=0.05). There was a nonsignificant difference (p= 0.62) between normal ECG groups when compared with abnormal ECG regarding sex as there was a female predominance in both groups (Table 1).

	Normal ECG	Abnormal ECG	P-value
Age	30.87± 12.107	38.09± 15.733	0.04(S)
Disease duration	3.152± 2.2332	5.117± 4.5852	0.05(S)
Female sex	87.2%	87.0%	0.623

Table 1. Comparison between the two groups regarding age, disease duration and sex

There was a nonsignificant difference (p=0.6) between both groups regarding family history as most of the patients in both groups had a negative family history.

Regarding ANA, there was a nonsignificant difference (p = 0.34) between both groups regarding ANA profile and ANA pattern but there was a significant difference (p = 0.04) between both groups regarding ANA titer. There was a nonsignificant difference (p = 0.34) between both groups regarding Anti nucleosome, Anti dsDNA, Anti histone, Anti smith, Anti RNP, Anti SCL70, Anti PCNA, Anti ribosomal, Anti DFS70. We found that there was a nonsignificant difference between both groups regarding the SLEDAI score (table 2).

		Normal ECG	Abnormal ECG	P-value
ANA profile	Positive	68.1%	56.5%	0.343
ANA pattern	Homogenous	23.4%	26.1%	0.722
	Homogenousand speckled	2.1%	0.0%	
	Negative	34.0%	39.1%	
	Nucleolar	4.3%	0.0%	
	Ribosomal	2.1%	4.3%	
	Speckled	34.0%	30.4%	
Individual ANAs	Anti nucleosome	27.7%	17.4%	0.347
	Anti dsDNA	40.4%	21.7%	0.122
	Anti histone	12.8%	4.3%	0.413
	Anti smith	19.1%	4.3%	0.149
	Anti RNP	14.9%	4.3%	0.257
	Ant SCL70	0.0%	4.3%	0.32
	Anti PCNA	2.1%	0.0%	0.67
	Anti ribosomal	4.3%	0.0%	0.29
	Anti DFS70	6.4%	0.0%	0.54
	Anti RO and LA	38.3%	56.5%	0.10

Table 2. The relation between ANA pattern and ECG findings in patient with SLE

In our study, 41.9% of positive Anti RO and LA patients had abnormal ECG but only 25.6% of negative Anti RO and LA patients had abnormal ECG, with a nonsignificant difference (table 3).

	Positive anti Ro/La	Negative anti Ro/La	P-value
Normal ECG	18(58.1%)	29(74.4%)	0.10
Abnormal ECG	13(41.9%)	10(25.6%)	
Total	31	39	

Table 3. ECG abnormality in patients with positive Anti RO and LA

We found that mean age within positive Anti Ro patients older than negative patients, also ECG findings were more frequent in positive patients than negative Anti Ro and LA with a nonsignificant difference. By regression analysis, we found that only oral/nasal ulcers and Anti RO/LA positivity were an independent risk factor for abnormal ECG, but each of age and arthritis was dependent on risk factors.

When we made a correlation between SLEDAI and disease duration, we found that disease duration nonsignificant and positively correlated with the activity of the disease by SLEDAI score as shown in (table 4).

		SLEDAI Score
Disease duration	Pearson Correlation	0.007
	P_ value	0.957
	N	70

Table 4. Correlation between disease duration and SLEDAI score

Discussion

Our study included 70 SLE patients, divided into two groups, the first group included 32.9% of cases had abnormal ECG findings, and the second group included 67.1% had normal ECG. Regarding ECG findings, we found that 17.1% of our patients had ischemia, 12.9% had sinus tachycardia, and only 1.4% had left bundle branch block, these results were in agreement with ***Menendez et al. (6)*** who said that common ECG abnormality was CHB and ischemia.

In this study, we found that mean age of patients had abnormal ECG was older than normal ECG patients (38.09, 30.87 respectively) with significant difference (p=0.04), also in the study of ***Agmon-Levin et al. (7)*** average age of patients with SLE with cardiac problems was 31.5 years (range 18 to 54 years). In the current study mean duration of disease was longer in patients had abnormal ECG than normal ECG patients with significant difference (p=0.05). Resembling our findings, ***Tanaka et al. (8)*** reported that there is a relationship between anti-SSA/Ro antibodies positivity and ECG abnormality, and late_ onset of SLE (average age of 50) was suggested.

We found that there was a nonsignificant difference (p= 0.62) between normal ECG groups when compared with abnormal ECG regarding sex as there was a female predominance in both groups. Furthermore, there was a nonsignificant difference (p = 0.6) between both groups regarding family history as a majority of patients in both groups had a negative family history (93.6%, 95.7% respectively), also in the study of ***Agmon et al. (7)***, there was female dominance as it included 11 females and 1 male.

In this study, we found that there was a significant difference (p = 0.006) between both groups regarding oral ulcers as the majority of patients in both groups had positive oral ulcers (83%, 52.2% respectively) but we found that there was no significant difference between both groups concerning other cutaneous manifestations, while there was a significant difference (p = 0.03) between both groups regarding arthritis as most of the patients in both groups had positive arthritis (91.5%, 69.6% respectively).

Similar to our results, ***Cimaz et al. (9)*** observed that repeatedly manifestations in their study were cutaneous rash and oral ulcers, ***Menendez et al. (6)*** reported that ECG abnormality is more frequent in arthritis and CLE. even so, the pattern with both anti-SSA/Ro60 and anti-Ro52/TRIM21 is more frequently associated with SCLE, and anti-Ro52/TRIM21 is more strongly related to CHB. In contrast,

Fukuda et al. (10) and Yoshimi et al. (11) found that Anti-SSA/Ro antibodies and ECG abnormality show a relationship with cutaneous vasculitis, photosensitivity, SCLE, and hematological disorders (anemia, leukopenia, and thrombocytopenia) (10, 11).

Furthermore, we found that there was a nonsignificant difference (p = 0.2) between both groups regarding Psychosis/seizures as a majority of patients in both groups had negative Psychosis/seizures (97.9%, 91.3% respectively).

Moreover, we found that there was a nonsignificant difference between both groups regarding all cardiopulmonary manifestations as a majority of patients in both groups had negative cardiopulmonary manifestations except dyspnea as a majority of both groups had dyspnea.

There was a nonsignificant difference between both groups regarding laboratory investigations (CBC, liver and renal functions, ESR, and p/c ratio). There was a nonsignificant difference between both groups regarding proteinuria and cast as majority as patients in both groups had nor proteinuria or cast. There was a nonsignificant difference (p = 0.34) between both groups regarding the ANA profile as a majority as patients in both groups had positive ANA (68.1%, 56.5% respectively). But contrary to ours, ***Fukuda et al. (10) and Yoshimi et al. (11)*** found that Anti-SSA/Ro antibodies and ECG abnormality correlate with hematological disorders (anemia, leukopenia, and thrombocytopenia).

In the current study, there was a nonsignificant difference (p = 0.72) between both groups regarding ANA pattern as a majority as patients in both groups had negative ANA followed by a speckled pattern. Autoantibodies, such as endothelial anti cells, anti-SSA/Ro, or anti-phospholipid antibodies were found to be correlated with cardiac involvement in many autoimmune diseases(12). The occurrence of heart failure in these patients may be due to a combination of many factors such as nephritis, hemodynamic overload, or due to some drugs, for example, high doses of steroids or some cytotoxic medications (13).

In our study, there was a nonsignificant difference (p = 0.34) between both groups regarding other autoantibodies, most of the patients in both groups had negative Anti nucleosome, Anti histone, Anti dsDNA, Anti smith, Anti RNP, Anti SCL70, Anti PCNA, Anti ribosomal, and Anti DFS70.

As regards the disease activity index, we found that there was a nonsignificant difference between both groups regarding the SLEDAI score.

As regards the relation between ECG abnormality and Anti RO and LA, we found that 41.9% of patients who had positive anti_ RO and LA had abnormal ECG findings, while 58.1% of them had normal ECG. In line with our results, ***Higuera-Ortiz et al. (14)*** compared SLE patients with either anti-Ro⁄SSA-positive or negative with healthy controls and found a higher pervasiveness of conduction system abnormalities in the anti- Ro positive group than in the other two groups.

In agreement with our results, previous studies have verified that in lupus patients, anti-Ro/SSA antibodies are correlated with the incidence of an atrioventricular block (15, 16). Similar to our results, adult systemic lupus erythematosus patients with anti-Ro/SSA antibodies have been documented to have a temporary or CHB in a study of ***Lim et al. (17) and Arce-Salinas et al. (15)***. Anti-Ro antibodies can cause many things as calcium channelopathy, electrophysiological effects of the myocardium, and inflammation are due to the pathogenesis of anti-Ro/SSA (16). In calcium channelopathy theory, ***Lazzerini et al.***

(18) demonstrated the arrhythmogenic impact of anti-Ro/SSA antibodies on the heart of adults that could be linked to an irregular system of calcium channels, that can be expressed in the atrioventricular and sinoatrial nodes. Higher calcium channel funds and lower intrinsic sensitivity of adult cardiomyocyte may have a role in conduction system tissue damage. Calcium and fibrous tissue are deposited at many parts of conduction systems especially A-V node. Fibroblasts can also considerably lessen electrical coupling, whereas also reducing the spread of the conduction system and blocking it, which may be a cause of adult patients CHB. The anti-Ro/SSA antibodies electrophysiological effect on myocardium has also been reported (19).

Also, ***Sung et al. (20)*** reported that clinical myocarditis in 3 to 15% of SLE patients can be precipitated by anti-Ro/LA antibodies. In a cohort of about 60 patients who have many types of CTD, ***Lazzerini et al. (18)*** and ***Lazzerini et al. (21)*** found that about (58%) of patients with positive anti-Ro ⁄ SS had a prolongation in QTc, with a mean QTc duration notably longer in anti-Ro ⁄ SSA-positive than negative patients, with a significant p-value. The effect of anti-Ro⁄SSA on QTc was highly selective (21). In a further study, ***Lazzerini et al. (22)*** analyzed patients with CTD, nearly half of them were anti-Ro⁄SSA positive using an ambulatory 24-hour ECG monitoring system: the previous study, persistent QTc prolongation throughout the daytime was observed in 46% of positive compared to only 5% of the Anri Ro/SSA negative patients. The most remarkable finding of their study was that the incidence of complex ventricular arrhythmias (additionally including scenes of unsustained ventricular tachycardia) in anti_ Ro⁄SSA antibodies positive patients was five times as that in the negative 0ne, with a noteworthy direct relationship in the entire populace between the length of the mean worldwide 24-h QTc and ventricular arrhythmic burden (freely from age and disease duration) Even though the prior examinations recommended the presence of an immune-mediated mechanism that affects the arrhythmogenicity of the heart in anti-Ro ⁄ SSA-positive patients, two diverse studies detailed in part clashing outcomes. In the first, rather than our discoveries, ***Costedoat-Chalumeau et al. (23)*** didn't show any noteworthy distinction in mean QTc interval when contrasting SLE patients with anti-Ro⁄SSA-positive versus those with anti-Ro/SSA negative antibodies. In another study done by ***Gordon et al. (24)***, the outcomes were somewhat different. As confirmed by the authors, despite the fact that, for this situation, no noteworthy contrast emerged between the two groups; anyway the mean QTc was marginally longer in positive patients, and this distinction was very near to the statistical significance (P = 0.063). Similar to our results, there is dissonant information in regards to the relationship between anti_ SSA/Ro titers, ECG results, and the activity of the disease, yet it appears that anti_ SSA/Ro antibodies levels will in general decrease when patients are treated with cytotoxic medications (7, 25). Also, ***Higuera-Ortiz et al. (26)*** retrospectively verified that the titers of anti-Ro antibody changed in relation to certain SLE disease activity types, in particular, serositis. However, it was concluded that the duration of the increases and decreases in anti-Ro antibody titers appeared to be longer compared to other antibodies.

In contrast to our findings, ***Higuera-Ortiz et al. (14)*** found no association between anti-Ro/LA antibodies and cardiac manifestations in patients with

SLE. Also, ***Lazzerini et al. (27)***on 33 patients with SLE, and by ***Gordon et al. (24)*** on 111 female patients with different CTD (mainly SLE) did not demonstrate any relation between circulating anti-Ro ⁄ LA antibodies and abnormalities in the conduction system.

When we made regression analysis, we found that only oral/nasal ulcers were the independent risk factor for abnormal ECG, but each of age and arthritis was dependent on risk factors. Also, we made a connection between disease duration and SLEDAI score, we found that disease duration nonsignificant and positive linked with disease activity by SLEDAI score.

Conclusion:

Recent evidence showed that the grown-up heart may speak to an objective of anti_ Ro⁄SSA antibodies' arrhythmogenicity. Notwithstanding, the particular rhythm disturbances happened to appear to be age _related, as saw that ventricular repolarization variations from the norm (specifically QTc prolongation) were the overwhelming finding in the grown-ups, the contribution of the conduction system is for all intents and purposes limited to the fetal heart as it were

In spite of the fact that the precise arrhythmogenic mechanisms have not been explained so far, increased incidence suggest that anti-Ro ⁄ SSA antibodies may elicit changes in the rhythm throughout a repressing cross-reaction with a few cardiovascular ionic channels, especially the calcium channels (L-type and T-type), yet besides, the potassium channel hERG, whose different expression and involveement in electrophysiology of the heart in life expectancy may represent the incidence of age-related differences.

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