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Exploring the Significance of Elevated Antinuclear Antibodies in Medically Critically Ill Patients

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ABSTRACT: Antinuclear antibodies (ANA) and a type of antibodies that are produced against macromolecules in cell nuclei or the cytoplasm. Indirect immunofluorescence is the most widely method to detect ANA with additional solid phase assays also being available. All the patient admitted to the ICU and had their ANA levels drawn at the SMDC within the past three years (Jan 2017 to Dec 2019) were included in the study. In patient with multiple hospitalizations, the most recent one was considered for the study. ANA levels were detected using immunofluorescence assay technique. Between Jan 2017 and Dec 2019, 600 patients had their ANA levels drawn, out of which 78 were positive and 522 were negative. Out of the ANA positive patients, 14 (17 percent) had the values to 1:40, 29 (35 percent) had values to 1:80, 14 (17 percent) had values to 1:160, 8 (9.7 percent) had values to 1: 320, 11 (13.2 percent) had values to 1:640, 4 (4.8 percent) had values to 1:1280, 2 (2.4 percent) had values greater than >1:1280. It is concluded that in patients with RA, important differences exist between those who are ANA-positive and ANA-negative in terms of time to fulfillment of RA criteria and time to DMARD initiation as well as choice of initial pharmacotherapy.

KEYWORDS: Antinuclear antibodies, SMDC.

INTRODUCTION:

Antinuclear antibodies (ANA) and a type of antibodies that are produced against macromolecules in cell nuclei or the cytoplasm. Indirect immunofluorescence is the most widely method to detect ANA with additional solid phase assays also being available.

ANA autoantibodies are most commonly used to diagnose connective tissue diseases like SLE, systemic sclerosis and Sjogren's syndrome with their sensitivity varying with dilution. They are for instance 100 percent sensitive for Systemic sclerosis at a dilution of 1:40 and 87 percent sensitive at a dilution of 1:160. At the same time, they can be detected in 32 percent of normal population at a dilution of 1:40, with their prevalence dropping to 5 percent at 1:160 [1].

Anti nuclear antibodies can also be elevated in a number of other causes other than rheumatological illnesses like other autoimmune diseases (hashimoto thyroiditis, autoimmune hepatitis, primary biliary cirrhosis), infections like EBV, HIC, HCV, syphilis and lymphoproliferative malignancies. In addition, some medications like procainamide, hydralazine can also elevate ANA levels [2].

Although ANA are studies extensively for their utility in diagnosis of rheumatological illnesses and their presence in other clinical scenarios listed above, there is a very limited date on their significance when elevated in critically ill patients [3]. The purpose of our study is to see what is the prevalence and common probable causes for elevated ANA in critically ill patients and if there is any difference in their interpretation in critically ill patients. The primary outcome was hospital mortality, and secondary outcomes included duration of mechanical ventilation and MICU length of stay [4].

METHODS

Screening

All the patient admitted to the ICU and had their ANA levels drawn at the SMDC within the past three years (Jan 2017 to Dec 2019) were included in the study. In patient with multiple hospitalizations, the most recent one was considered for the study. ANA levels were detected using immunofluorescence assay technique. Patient with multiple ANA levels during the same admission, the highest value was recorded for the study.

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Data collection

Baseline demographics (age, race and gender), WBC count, neutrophil percentage, hemoglobin level, platelet count. Manual chart review was formed to collect date on the presence of medical comorbid illnesses including acquired immune deficiency syndrome/human immune deficiency virus (AIDS/HIV) infection, hypertension (HTN), diabetes mellitus (DM), obstructive airway disease (OAD), chronic liver disease (CLD), congestive heart failure (CHF), coronary heart disease (CAD), chronic kidney disease (CKD), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), other rheumatological diagnosis. The admitting diagnosis of the patients were also recorded and were classified into Cardiac, GI, metabolic, neurological, pulmonary, obstructive airway disease, pulmonary, renal, sepsis/septic shock, and hematological.

APACHE score and ICU Outcomes

The Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) derived risk of death during the hospitalization was determined from the worst values obtained during the 24 hours of MICU admission. Utilization and duration of invasive mechanical ventilation, ICU length of stay (LOS) and hospital mortality were also collected. Length of stay in the MICU was defined as the time from ICU admission to time of transfer out of the MICU.

Rheumatological serologies:

Additional data collected included further testing of done for anti double-stranded DNA antibodies (anti-DsDNA), anti-smith antibodies, anti-U1-RNP antibodies, anti-Ro antibodies, anti-La antibodies, ant ribosomal P antibodies, antitopoisomerase-1, anticentromere antibodies, anti-jo-1 antibodies, Rheumatoid factor, Anti-cyclic citrullinated peptide antibodies and anti histone antibodies.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistic Version 21 (IBM Corp and others, 1989, 2013). Continuous normally distributed variables were reported using means and standard deviation. They were compared between the groups using t-test. If the normality was not met the rank Kruskall-Wallis test was applied instead. Equality of variances was testes using Levenes's test. Continuous not normally distributed variables were reported using median, first and third quartile (Q1 and Q3).

RESULTS

Between Jan 2017 and Dec 2019, 600 patients had their ANA levels drawn, out of which 78 were positive and 522 were negative. Out of the ANA positive patients, 14 (17 percent) had the values to 1:40, 29 (35 percent) had values to 1:80, 14 (17 percent) had values to 1:160, 8 (9.7 percent) had values to 1: 320, 11 (13.2 percent) had values to 1:640, 4 (4.8 percent) had values to 1:1280, 2 (2.4 percent) had values greater than >1:1280. Baseline demographics and clinical characteristics are given in Table 1.

Table 01. Baseline demographic, clinical and laboratory variables comparison with respect to ANA Group.

	High n=37	Low N=41	ANA - (n= 522)	P-value
Age ,Median (IQR)	57 (46.5- 66.5)	56 (45.5-66.5)	56 (42 – 67)	0.972
Sex (Females), n(%)	27 (73%)	25 (61%)	253 (48%)	0.006
Admission Diagnosis, N (%)				
1 2 3 4 5 6	5 (13%) 2 (5%) 2 (5%) 4 (11%) 1 (3%) 9 (24%)	1 (2%) 5 (12%) 5 (12%) 6 (14%) 4 (10%) 8 (19%)	44 (8%) 84 (16%) 33 (6%) 73 (14%) 19 (3%) 113 (21%)	

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7 8 9 10	3 (8%) 8 (21%) 1 (3%) 2 (5%)	2 (5%) 4 (10%) 0 (0%) 6 (14%)	26 (5%) 83 (16%) 4 (1%) 43 (8%)	0.415
Admission APACHE Score, Median (IQR)	17 (12.5-27)	16 (10.5-24.5)	16 (10-24)	0.291
Therapies/Interventions, N (%)				
Prior steroids	13 (35%)	6 (14%)	52 (10%)	<0.001
Prior immunosuppressive therapy	4 (11%)	0 (0%)	3 (1%)	<0.001
Baseline Comorbidities/Risk factors, N (%)				
AIDS/HIV	1 (3%)	6 (14%)	83 (16%)	0.094
HTN	23 (62%)	21 (51%)	299 (57%)	0.615
DM	14 (38%)	12 (29%)	142 (27%)	0.373
OAD	10 (27%)	13 (32%)	136 (26%)	0.730
CLD	71 (12%)	7 (9%)	64 (12%)	0.402
CHF	3 (8%)	4 (10%)	78 (15%)	0.686
CAD	6 (16%)	3 (7%)	57 (11%)	0.449
CKD	6 (16%)	6 (14%)	94 (18%)	0.838
SLE	9 (24%)	1 (2%)	4 (1%)	<0.001
RA	3 (8%)	2 (5%)	3 (1%)	<0.001
Other Rheum	3 (8%)	1 (2%)	9 (2%)	0.036
Baseline Labs, Median (IQR)				
HB	10.5 (9.05 -12.6)	11.6 (10.5 -12.95	11.7 (9.1-13.45)	0.181
Platelet count	228.5 (111.75-299.5)	257 (157-313.5)	195.5 (132 -274.75)	0.132
Albumin, serum	3.5 (2.7- 3.8)	3.7 (3-4.2)	3.6 (3-4.1)	0.250
Lymphocyte (count in blood)	12.5 (6.85-24.1)	11.8 (8.25-21.8)	13.2 (7.2 - 22.73)	0.983
Serum Creatinine	1.3 (0.85-2.65)	1.2 (0.8-1.7)	1.1 (0.8- 2.2)	0.648

DISCUSSION

There is limited evidence that suggests that the presence of ANA antibodies in general population is not associated with an increased risk of cancer or mortality [5]. A study consulted by Selmi et al. looking at randomly selected 2828 subjects from a norther Italian region found that while the patients with positive ANA levels were more likely to develop connective tissue disorders, there was no increases risk of mortality or development of cancer in the patients with elevated ANA levels [6-8]. To our knowledge here has not been any studies looking at the hospital or ICU outcomes in patients based on their ANA Levels. A metanalysis of case reports and case series conducted by Quintero et al. on patients with autoimmune disease admitted to the ICU, found the mortality to range from 17 to 55 percent in patients with all autoimmune diseases [9]. They found that the studies looking on the patients with specific autoimmune illnesses, like SLE, mortality was as high as 79 percent. High APACHE score, multi-organ dysfunction, older age and cytopenia were the most reported variables associated with increased mortality [10].

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A number of studies have looked at the frequency of positive ANA tests in "healthy" individuals. A study by Arroyave et al. in 1988 [3] screened sera from 241 "normal" children, testing for only IgG ANA, using both mouse kidney and human epithelial cells (HEp-2 cells). The study found a maximum positivity rate of only 2.0% at the lowest dilutions. However, data from adult studies have found much higher rates. In an adult study from 15 international laboratories using HEp-2 cells as substrate [11], ANA positive tests occurred in 31.7% of a putatively normal population at a serum dilution of 1:40. Even at a dilution of 1:320, 3.3% of the sera were positive. Interestingly the ANA frequency did not differ significantly across the age range of 20-60 years. The rate of ANA positivity among blood donors in Holland was also quite high at 12.7%, with titers greater than 1:80 occurring in over 4% [12].

CONCLUSION

It is concluded that in patients with RA, important differences exist between those who are ANA-positive and ANA-negative in terms of time to fulfillment of RA criteria and time to DMARD initiation as well as choice of initial pharmacotherapy.

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