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Evaluation of some biochemical markers in alopecia areata

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Abstract
Background: It has recently evidenced that autoimmune diseases are associated with concurrent activation of inflammation, immune system, and coagulation. Given that alopecia areata (AA) is an autoimmune disease, there is a possibility that inflammation and coagulation processes may participate in the disease pathogenesis and could be associated with patients' poor outcome. The aim of this work was to investigate the serum levels of some biochemical and hematological markers reflecting the inflammatory and coagulative status, as well as the thyroid functions in patients with AA.
Patients and Methods: This study included 25 patients with AA and an equal number of matched healthy individuals. The study patients underwent laboratory investigations including erythrocyte sedimentation rate (ESR), complete blood count (CBC), C-reactive protein (CRP), fibrinogen, D-dimer, and thyroid stimulating hormone (TSH).
Results: Statistically significant lower MCH and platelets count, and higher WBCs count, ESR, CRP, D-dimer, and TSH were seen in patients with AA. Receiver Operating Characteristic Curve (ROC) revealed that all these markers were of predictive value of the disease occurrence. The CRP and D-dimer levels showed the best diagnostic performance with sensitivities of 92% for both, and specificities of 80% and 76%, respectively.
Conclusion: This study supports the association between the coagulation system dysfunction, acute inflammatory state, and auto immune reactions in AA.

Keywords: Alopecia areata (AA), autoimmune disease, inflammation, coagulation, thyroid functions

Introduction
After androgenetic alopecia, AA is the second most prevalent type of non-scarring hair loss. It often manifests as oval or circular patches of hair loss. Relapse occurs frequently, whether or not a patient is receiving treatment. The disease prognosis is unpredictable. However, long-term hair loss (more than 10 years), nails affection, and positive family history are related to poorer prognosis [1].
The etiopathogenesis of AA is still not completely elucidated, but there are many factors that are thought to be possible contributors, including genetic predisposition, keratinocyte degeneration, immunological factors, infections, neurological disorders, and mental stress [2]. Additionally, it has been discovered that AA is linked to thyroid dysfunction [3].
Elevation of some inflammatory biomarkers, including tumor necrosis factor (TNF) and several interleukins, are shown in individuals with AA, indicating that they are crucial to the disease pathophysiology. All of these changes lead to hair follicle's inflammation, and subsequently, hair loss [4].
The parameters of CBC have been assumed as markers of inflammatory disorders [5]. Also, the tests most frequently employed to show the degree of inflammation are the ESR and CRP concentrations [6]. These markers have been investigated in relation to numerous autoimmune or inflammatory dermatologic disorders, either individually or together [7].
In addition, coagulation markers as (D.dimer and Fibrinogen) are found to be elevated in some autoimmune or inflammatory skin diseases suggesting interaction role between inflammation and coagulation in the pathogenesis of these diseases [8].
The aim of this work was to investigate the serum levels of some biochemical and hematological markers reflecting the inflammatory and coagulative status, as well as the thyroid functions in patients with AA.

Patients and Methods

This is an observational case-control study that was conducted at Tanta University Hospital in the period from March 2021 to July 2022 after approval by Local Ethical Research Committee in Tanta Faculty of Medicine, Code No: (34505/2/21), and per the declaration of Helsinki. The study included patients who were newly diagnosed with AA and those who did not receive treatment for at least one month. An equal number of healthy individuals were included as the control group.

Patients with dermatologic diseases other than AA, other autoimmune diseases, active infection, immunodeficiency, or malnutrition ***.were excluded from the study***Pregnant and lactating women, and those who were on regular medication were also excluded. Informed written consents were obtained from the included patients.

The included patients underwent full history taking, including the clinical disease history and family history. Patients were subjected to precise general examination and dedicated dermatological assessment, including a dermoscopy examination, to assess the site, number, and severity of lesions.

The severity of AA was estimated using a mathematical protocol used to assess the percentage of hair loss, which is the Severity of Alopecia Tool (SALT). It is estimated by determining the site of affection, where vertex affection represents a percentage of 40%, posterior profile affection represents a percentage of 24%, and both the left and right profiles affection represents 18% for each. The total score is obtained by adding the percentages of affected portions, and then the patient score ranged from S1 to S5 according to the total score [9].

Laboratory Examination

A total volume of 10 ml of venous blood was withdrawn through the antecubital fossa under complete aseptic conditions. A volume of 3 ml was transferred to an EDTA-containing tube for CBC analysis: it was performed by SysmexKX-21N, Sysmex Corporation, New York, USA to estimate hemoglobin (Hb) level and blood indices [10].

A volume of 7 ml was transferred to a plain tube, centrifuged, and separated. Serum samples were obtained and used for analyzing the CRP and D-dimer utilizing latex agglutination by immuneturbidimetry method test at 340 and 570 nm, respectively [11]. Serum fibrinogen was estimated based on the coagulation time [12]. For ESR estimation, the Westergren's method was used [13]. Measuring TSH was performed using Cobas ECLIAs (Roche Diagnostics GmbH, Mannheim, Germany) [14].

Study outcomes

The primary outcome was the difference in the laboratory markers between patients with AA and the control participants. The secondary outcome was the association between serum laboratory markers levels and the clinical aspects of patients with AA.

Statistical analysis

The patients' data were analyzed using the SPSS statistical software, version 20.0. (IBM, Armonk, NY: IBM Corp). Data normality was tested using The Shapiro-Wilk test, and then the data were represented accordingly. Chi-square test, Fisher's Exact, student t-test, Mann-Whitney test, and Spearman correlation test were used as appropriate. Receiver operating characteristic curve (ROC) was employed ***to*** determine the*of the* ***potential diagnostic value*** *was 0.05 value of less than-investigated markers. p .considered statistically significant*

Results

This study included 25 patients with AA and an equal number of matched healthy individuals. Patients' basic data are demonstrated in table 1. No statistically significant difference was found between the two groups regarding the age (p=0.285) or sex distribution (p=0.571).

The disease duration ranged from 0.5 to 420 months. Six cases (24%) had a positive family history of AA. Five types of AA were encountered in the patients. In order of prevalence, those were multiple patchy AA in 12 patients (48%), single patchy AA in 6 patients (24%), alopecia universalis (AU) in 3 patients (12%), ophiasis in 2 patients (8%), and alopecia totalis (AT) in 2 patients (8%). Ten patients (40%) presented with nail changes, the changes were in the form of fine pitting which was shown in 6 patients (24%) and fine pitting with longitudinal ridging occurred in 4 patients (16%) (Table 2).

Dermoscopic examination showed that, in order of frequency, 22 cases (88%) had vellus hair, 20 cases had yellow dots (80%), 18 cases (72%) had regrowing hair, 16 cases (64%) had black dots, 14 cases had exclamation marks (65%), and one case had pigtail hair (4%) (Table 2).

Disease severity assessment by SALT revealed that the highest percentage of the patients were of S2 (10 patients; 40%), followed by S1 scores (7 patients; 28%). Five patients had S5 score (20%), and 3 patients had S3 score (12%).

Concerning the laboratory investigations, no statistically significant differences were found in the hematocrit% (p=0.284), the RBCs count, and the mean MCV values. Statistically significantly lower MCH (p=0.019), MCHC (p=0.026), hemoglobin levels (p=0.002), and the platelets count (p=0.013), and higher WBCs count (p=0.010) were noted in patients group compared to the control group (Table 3). ROC analysis illustrated that MCH, platelets and WBCs had a good value in evaluation of prognosis of AA with AUCs of 0.674, 0.704, and 0.686, respectively (Table 4). The ESR levels showed statistically significant higher values in patients than the control group (p=0.002 and <0.001 in the first and second hours, respectively) (Table 3). The ROC analysis illustrated that the 1st and 2nd hours readings could aid in the diagnosis of AA with AUCs of 0.751, and 0.853, respectively (Table 4).

The mean CRP and d-dimer levels were significantly higher in the patients group (p<0.001 for both) (Table 3). The ROC analysis showed that both of them could help in evaluation of severity and prognosis of AA with AUCs of 0.953, and 0.927, respectively (Table 4).

The mean TSH value in the patient group was significantly lower than the control group, with a p value of 0.002 (Table 3). The ROC analysis illustrated that TSH could confirm the diagnosis of AA with AUC of 0.755. (Table 4). No statistically significant difference was found in the fibrinogen level (Table 3).

The duration of the disease differed significantly according to the presence of black dots (p<0.001), exclamation marks (p<0.001), and regrowing hair (p=0.001). Statistically significant differences were found in the SALT scores according to the presence of black dots (p=0.001), exclamation marks (p=0.001), and regrowing hair (p=0.002) (Table 5). There was no statistically significant correlation between SALT scores and other parameters (Table 6).

Discussion

Alopecia areata is a complex multifactorial disorder with an uncertain prognosis. Despite the spontaneous healing seen in several patients, the disease may progress to a chronic condition in some patients. Several hypotheses have been introduced regarding AA pathogenesis, with inflammation and coagulation processes are main contributors [15].

Complete blood count measurement is an easy and low-costing laboratory tests. It provides a crucial evidence of systemic inflammatory process [16]. In the current work, the CBC analysis of the studied group demonstrated statistically significant lower MCH and platelets count, and higher WBCs count. Moreover, ROC analysis revealed that MCH, platelets and WBCs count could aid in evaluation of disease activity and its prognosis with AUCs of 0.674, 0.704, and 0.686, respectively. These findings are in harmony with the established association between autoimmune diseases and anemia, leukocytosis as well as thrombocytopenia [17]. The possible explanations are that in active inflammatory diseases, absorption of iron is limited and not distributed to the bone marrow resulting in a chronic anemia unless the inflammation is controlled. This is expressed in falling in hemoglobin parameters including MCH. Also, leukocytosis is known to manifest in response to the inflammatory stressor/cytokine cascade, which is the case in AA. In addition, some autoimmune diseases are associated with anti-platelet antibodies causing peripheral destruction and decreased platelet count [18]. In the context of AA, only one study could be reached evaluating CBC in patients with AA, this was conducted by İslamoğlu & Demirbaş (2020). They reported that, the difference in CBC parameters did not reach the level of significance, which disagrees with the findings of the present study [19].

In addition, ESR and the CRP concentrations often exhibit the severity of inflammatory process [6]. Recently, these markers have shown association with other dermatological diseases [5, 20-22]. These data supporting the findings in the current study, where both markers were significantly elevated in our patients with AA. Obviously, ESR at the first and the second hours were found to predict AA severity and prognosis with AUCs of 0.751, and 0.853, respectively, and CRP could help in evaluation and management of AA with AUCs of 0.953. However, the study İslamoğlu & Demirbaş (2020) found only significant elevation in the CRP levels [19].

Regarding the relation between the inflammation and coagulation, pro-inflammatory cytokines that increase in AA such as IL-6 and TNF have been presumed to initiate coagulation through expression of the tissue factor. In turn, the coagulation-related proteases affect the protease-stimulated receptors, which induce the expression of several inflammatory cytokines that trigger the inflammation process. The pathologic pathway is amplified and kept activated by the cross-talk among the inflammation, immune system, and coagulation [7]. Activating the coagulation cascade results in fragmenting the fibrin into the fibrin degradation products (FDPs), including the most clinically significant product; d-dimer. D-dimer elevation denotes forming stable fibrin, and indicates the initiation and activation of fibrinolysis and coagulation [23].

In the present work, significantly higher D-dimer levels were noted in the studied patients, and ROC analysis revealed that D-dimer could aid in evaluation and managment of AA with AUCs of 0.927. This is in consistency with previous studies that established an association between the coagulation system dysfunction and the autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus that revealed an elevated thrombosis risks [24, 25]. Interestingly, the D-dimer levels were assessed in latest study of Shakoei *et al*. (2021) which, in congruence with this study, reported that the plasma levels of D-dimer were shown to be higher in AA patients [11]. This study showed no statistically significant correlation between CBC parameters, CRP, ESR or D dimer and SALT scores of the patients. This is likely attributed to the small sample size. In the study of Shakoei *et al*. (2021), d-dimer was also found to be not significantly correlated with SALT score [11].

The present study evaluated TSH levels and demonstrated significantly lower levels in patients than controls and ROC analysis revealed that TSH could confirm the autoimmune theory of AA with AUC of 0.755. These findings are in agreement with the study of Baars *et al*. (2013) who reported AA association with thyroid diseases and recommended assessing AA patients with thyroid function tests and autoantibody tests in daily practice [26]. Also, the study of Saniee *et al*. (2019) reported prevalence ranged from 8% to 28% of thyroid disorders in AA patients [27].

Table 1: Comparison between the patients and controls according to age and sex

Clinical data	AA Patients (n = 25)		Controls (n = 25)		Test of sig.	p
	No.	%	No.	%		
Sex						
Male	14	56.1	12	48.0	X^2= 0.321	0.571
Female	11	44.0	13	52.0		
Age (years)						
Min. – Max.	15.0 – 48.0		19.0 – 46.0		U=257.5	0.285
Mean ± SD.	27.26 ± 11.59		27.56 ±8.64			
Median (IQR)	20.0 (17.0 – 37.0)		25.0 (22.0 – 27.0)			

AA: alopecia areata, SD: Standard deviation, IQR: Inter Quartile Range, X^2: Chi square test, U: Mann Whitney test

Table 2: Distribution of the studied AA patients according to the clinical findings (n=25)

Clinical findings	AA Patients	
	N	%
Duration (months)		
Min. – Max.	0.50 – 60.0	
Mean ± SD.	19.36 ± 24.0	
Median (IQR)	5.0 (3.0 – 48.0)	
Family history		
Negative	19	76.0

Positive	6	24.0
Type of alopecia		
Universalis	3	12.0
Single patchy	6	24.0
Multiple patchy	12	48
Ophiasis	2	8.0
Totalis	2	8.0
Nail involvement		
No involvement	15	60
Fine pitting	6	24
Fine pitting with longitudinal ridges	4	16
Dermoscopic hair findings	**AA patients**	
	N	%
Black dots	16	64.0
Exclamation mark	14	56.0
Yellow dots	20	80.0
Vellus hair	22	88.0
Pig tail hair	1	4.0
Regrowing hair	18	72.0
Nail findings		
Nail fine pitting	6	24
Nail fine pitting with longitudinal ridges	4	16

AA: alopecia areata, N: number, SD: Standard deviation, IQR: Inter Quartile Range

Table 3: Comparison between patients and controls according to CBC results

CBC results	AA Patients (n = 25)	Controls (n = 25)	Test of sig.	p
Hemoglobin (gm/dl)				
Min. – Max.	8.40 – 15.80	11.10 – 15.90	t=3.34	0.002*
Mean ± SD.	11.98 ± 1.85	13.50 ± 1.33		
Median (IQR)	13.20 (12.10 – 14.30)	13.50 (12.60 – 14.20)		
Hematocrit%				
Min. – Max.	31.0 – 44.60	33.0 – 39.80	t=1.088	0.284
Mean ± SD.	38.20 ± 3.40	37.37 ± 1.78		
Median (IQR)	38.0 (36.10 – 40.30)	36.90 (36.90 – 38.90)		
RBCs count (x10^6/µl)				
Min. – Max.	3.76–5.04	3.67–4.94	t=0.98	0.42
Mean ± SD.	4.55±0.288	4.35±0.194		
Median (IQR)	4.45 (4.12-4.85)	4.4 (4.05-4.78)		
MCV (fl)				
Min. – Max.	61.96 – 88.37	73.0 – 88.0	t=0.664	0.510
Mean ± SD.	78.10 ± 6.83	79.16 ± 4.07		
Median (IQR)	78.10 (74.0 – 84.44)	78.0 (75.0 – 82.0)		
MCH (pg/cell)				
Min. – Max.	16.79 – 31.78	27.0 – 31.0	t=2.5*	0.019*
Mean ± SD.	26.58 ± 3.85	28.6 ± 1.32		
Median (IQR)	26.60 (25.35 – 28.55)	28.0 (27.0 – 30.0)		
MCHC (g/dl)				
Min. – Max.	27.09 – 37.37	33.0 – 40.0	U=198	0.026*
Mean ± SD.	33.92 ± 3.03	36.12 ± 2.19		
Median (IQR)	34.99 (32.96–36.01)	36.0 (35.0–37.0)		
Platelet x10^3				
Min. – Max.	167.0 – 500.0	190.0 – 352.0	U=185*	0.013*
Mean ± SD.	271.68 ± 85.31	298.96 ± 35.45		
Median (IQR)	253.0 (218.0–309.0)	301.0 (278.0–320.0)		
WBCsx10^3				
Min. – Max.	4.30 – 14.30	5.20 – 7.10	t=2.78*	0.01*
Mean ± SD.	7.42 ± 2.46	6.02 ± 0.57		
Median (IQR)	7.20 (5.60 – 8.90)	5.90 (5.60 – 6.40)		
1st hour ESR				
Min. – Max.	5.0 – 45.0	3.0 – 8.0	155.5*	0.002*
Mean ± SD.	12.60 ± 10.34	5.16 ± 1.121		
Median (IQR)	10.0 (5.0–15.0)	5.0 (4.0–6.0)		
2nd hour ESR				
Min. – Max.	10.0 – 80.0	8.0 – 15.0	92.0*	<0.001*
Mean ± SD.	26.68 ± 18.96	11.8 ± 2.0		
Median (IQR)	20.0 (12.0–35.0)	10.0 (9.0–12.0)		

CRP (mg/l)				
Min. – Max.	3.0 – 6.10	1.50 – 4.0	t= 7.956*	<0.001*
Mean ± SD.	4.56 ± 0.90	2.81 ± 0.63		
Median (IQR)	4.40 (4.0 – 5.30)	3.0 (2.50 – 3.20)		
D-Dimer (mg/l)				
Min. – Max.	50.0 – 400.0	20.0 – 140.0	U= 45.5*	<0.001*
Mean ± SD.	165.4 ± 78.54	78.8 ± 32.19		
Median (IQR)	150.0 (120.0 – 180.0)	80.0 (50.0 – 100.0)		
TSH				
Min. – Max.	1.82 – 6.12	0.57 – 4.15	U= 161.5*	0.003*
Mean ± SD.	3.14 ± 0.99	2.08 ± 1.22		
Median (IQR)	3.15 (2.51 – 3.52)	1.69 (1.14 – 3.17)		
Fibrinogen				
Min. – Max.	158.0 – 308.0	189.0 – 301.0	t= 0.148	0.883
Mean ± SD.	247.48 ± 38.89	249.1 ± 36.47		
Median (IQR)	257.0 (224.0 – 274.0)	250.0 (2122.0 –280.0)		

AA: alopecia areata, Hct: hematocrit, RBCs: red blood corpuscles, MCV: mean corpuscle volume, MCH: mean corpuscle hemoglobin, MCHC: mean corpuscle hemoglobin concentration, WBCs: white blood cells, SD: Standard deviation, IQR: Inter Quartile Range, t: Student t-test, U: Mann Whitney test, CBC: complete blood count

Table 4: Validity (AUC, sensitivity, specificity) for studied markers to discriminate AA patients (n = 25) from controls (n = 25)

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
MCH (pg/cell)	0.674	0.035*	0.511 – 0.836	≤27	52.0	72.0	65.0	60.0
Platelet ($x10^3$)	0.704	0.013*	0.546 – 0.862	≤263	60.0	88.0	83.3	68.7
WBCs (x103)	0.686	0.024*	0.519 – 0.853	>6.5	60.0	80.0	75.0	66.7
1st hour ESR	0.751	0.002*	0.614 – 0.888	>6	56.0	92.0	87.5	67.6
2nd hour ESR	0.853	<0.001*	0.747 – 0.958	>14	72.0	92.0	90.0	76.7
CRP (mg/l)	0.953	<0.001*	0.900 – 1.005	>3.2	92.0	80.0	82.1	90.9
D-Dimer (mg/l)	0.927	<0.001*	0.853 – 1.002	>100	92.0	76.0	79.3	90.5
TSH (mIU/l)	0.742	0.003*	0.593 – 0.890	>2.48	76.0	64.0	67.9	72.7

MCH: mean corpuscle hemoglobin, WBCs: white blood cells, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TSH: thyroid stimulating hormone, AUC: Area Under a Curve, CI: Confidence Intervals, NPV: Negative predictive value, PPV: Positive predictive value, *: Statistically significant at $p \leq 0.05$.

Table 5: Relation between SALT score and dermoscopic findings in AA patients (n = 25)

Dermoscopic findings	N	SALT score		U	p
		Mean ± SD.	Median (IQR)		
Black dots					
No	9	3.78 ± 1.48	5.0 (2.0 – 5.0)	17.5*	0.001*
Yes	16	1.69 ± 0.70	2.0 (1.0 – 2.0)		
Exclamation mark					
No	11	3.55 ± 1.44	3.0 (2.0 – 5.0)	17.0*	0.001*
Yes	14	1.57 ± 0.65	1.50 (1.0 – 2.0)		
Yellow dots					
No	5	1.80 ± 0.45	2.0 (2.0 – 2.0)	39.0	0.488
Yes	20	2.60 ± 1.57	2.0 (1.0 – 4.0)		
Vellus hair					
No	3	3.0 ± 1.73	2.0 (2.0 – 3.50)	24.0	0.497
Yes	22	2.36 ± 1.43	2.0 (1.0 – 3.0)		
Pig tail hair					
No	24	2.50 ± 1.44	2.0 (1.5 – 3.0)	–	–
Yes	1	1.0			
Regrowing hair					
No	7	4.14 ± 1.46	5.0 (3.5 – 5.0)	14.0*	0.002*
Yes	18	1.78 ± 0.73	2.0 (1.0 – 2.0)		

SALT: The Severity of Alopecia Tool, N: number, U: Mann Whitney test, *: Statistically significant at $p \leq 0.05$.

Table 6: Correlation between SALT score and different inflammatory and coagulation markers in AA patients (n = 25)

	SALT score	
	r_s	p
D-Dimer	0.390	0.054
CRP	0.187	0.370
ESR 1st hour	0.069	0.743
ESR 2nd hour	0.025	0.906
TSH	-0.008	0.970
MCH	0.012	0.956

Platelet x10^3	0.118	0.575
WBCsx10^3	-0.127	0.545

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TSH: thyroid stimulating hormone, MCH: mean corpuscle hemoglobin, WBCs: white blood cells, r_s: Spearman coefficient, *: Statistically significant at $p \leq 0.05$.

Conclusion

This study supports the association between the coagulation system dysfunction, acute inflammatory state, and auto immune reactions in AA.

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- All authors equally contributed to this work.

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