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Variability of Findings Due to Seasonal Alterations and Number of Attacks in Warm-Type Autoimmune Hemolytic Anemia

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Background: Examination of variability of findings due to seasonal alterations and variability of number of attacks in warm-type autoimmune hemolytic anemia (AIHA) was aimed in this study.
Materials and Methods: Patients over 18 years of age who were admitted to Ankara Numune Training and Research Hospital between 2009 and 2017 and were diagnosed with warm-type AIHA were included in this retrospective study. For statistical evaluation, SPSS 20 for Windows was used. For comparison of categorical data, chi-square and Fisher exact chi-square tests were used.
Results: The study population comprised 52 patients. The age range of the patients was 19-89 years, with a median of 45.5 years. Among the patients, the number of attacks was 1 in 63.5% (n=33), 2 in 15.4% (n=8), and 3 in 21.2% (n=11). The type of AIHA was the warm type in all of the patients. Concerning the season during which attacks were experienced, it was determined to be winter in 26.9% (n=14), autumn in 17.3% (n=9), summer in 38.5% (n=20), and spring in 17.3% (n=9) of the patients. The rate of attacks was determined to be higher during winter in the patient group with number of attacks of 2 or more and during summer and autumn in the patient group with number of attacks of 1 (p=0.030).
Conclusion: It was determined that, while the rate of patients who experienced only 1 AIHA attack increased during the summer and autumn seasons, attacks occurred commonly during winter in patients with more than 1 attack.
Keywords: Autoimmune hemolytic anemia, seasonal alteration, antibody

Introduction

Autoimmune hemolytic anemia (AIHA) is a disease characterized by the shortening of the lifespan of erythrocytes due to destruction through production of antibodies directed against the patient's own erythrocytes, anemia, and jaundice. There is an abnormal immune response in autoimmune hemolytic diseases, which turns the patient's own erythrocytes into targets of his or her own immune system. The incidence of AIHA is 1-3 in 100,000 in Western countries and its prevalence is 17/100,000 (1,2).

AIHA associated with warm antibodies is generally idiopathic. Apart from that, viral infections, collagen tissue disorders such as systemic lupus (SLE), medications, diseases associated with immunodeficiency, lympho-proliferative diseases, blood transfusion, and allogenic stem cell transplantation are factors blamed in its etiology (3).

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Autoimmune hemolytic disorders have some differences regarding the binding of antibodies to antigens. The binding of some antibodies at body temperature and of some antibodies at lower temperatures led to the differentiation of warm (37°C) and cold (<37°C) antibodies. Anti-globulin (Coombs) tests are of two types: direct tests and indirect tests. Bound antibodies and/or complements on a patient's erythrocytes are investigated in the direct Antiglobulin test and free antibodies in a patient's serum are investigated in indirect Antiglobulin test (4, 5).

Of AIHA cases, 70% are warm-type AIHA, caused by IgG antibodies and generally causing extravascular hemolysis. Warm antibodies are formed against Rh antigens. In more than 90% of the patients, a positive result with anti-IgG, anti-C_3, or both is revealed in direct or indirect Coombs tests. In the cold type, antibodies generally cause intravascular hemolysis, as they show their effects via complements, and these antibodies are generally of the IgM class (6, 7).

IgG can bind to erythrocyte surface antigen and the Fc receptor of cytotoxic cells. When complement is combined with an antibody, the third and fourth elements of the complement system bind to the erythrocyte membrane covalently and simultaneously to complement receptor on cytotoxic cells. This interaction may result in phagocytosis and lead to formation of spherocytes due to reduction of erythrocyte surface-to-volume ratio through partial or complete destruction of erythrocytes (8, 9).

Presentation in patients with AIHA is variable and depends on findings due to anemia, rate of development of anemia, compensative capacity of bone marrow, disease activity, and accompanying diseases. Paleness and jaundice are at the forefront in physical examination and splenomegaly may be detected. In the laboratory, reticulocyte count, serum lactate dehydrogenase, and indirect bilirubin levels are determined to be elevated and serum haptoglobin level is markedly decreased. In peripheral blood smears, spherocytosis and polychromatophilic erythrocytes are generally observed (10, 11).

Corticosteroids are included in the first-line treatment of warm-type AIHA and 70%-80% of the patients respond to the treatment. In the case of failure to respond or recurrence, splenectomy is considered. Patients have used multiple treatment modalities who are steroid-resistant or are found to respond to rituximab treatment by 45%-90%. Rituximab treatment combined with splenectomy has come into consideration (12, 13).

In studies conducted with patients with multiple sclerosis, SLE, type 1 diabetes mellitus, inflammatory bowel disease, and rheumatoid arthritis, disease incidence, presentation, and prognosis are shown to differ by seasons (14-20).

This study was planned since there has been no study on the seasonal association of warm-type AIHA that occurs by formation of anti-bodies against autoantigens and on how this association influences the course of the disease.

Materials and Methods

Patients over 18 years of age who were admitted to Ankara Numune Training and Research Hospital between 2009 and 2017 and were diagnosed with warm-type AIHA were included in this retrospective study.

Patients with cold-type and other AIHAs, patients under 18 years of age, and those with other autoimmune diseases were not included in the study. All of the patients included in the study were patients admitted from the Central

Anatolian Region of Turkey. The demographical data of all patients, their treatments, laboratory data, and time of AIHA attacks were recorded. Approval from the Ankara Numune Training and Research Hospital ethics committee was obtained.

Statistical Analysis

Statistical evaluation was performed using SPSS 20 for Windows (IBM SPSS Inc., Armonk, NY, USA). Normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. Numerical variables exhibiting normal distribution were represented as mean± standard deviation and numerical variables that did not exhibit normal distribution were represented as median (min-max). Categorical variables were represented as count and percentage. For determination of variables differing between attack number groups, ANOVA testing (post hoc: Bonferroni-corrected Student t-test) was used for numerical variables exhibiting normal distribution and Kruskal-Wallis test (post hoc: Bonferroni-corrected Mann-Whitney U test) was used for numerical variables that did not show normal distribution.

For comparison of categorical variables, chi-square and Fisher exact chi-square tests were used. The association between numerical variables was evaluated using Pearson and Spearman correlation. In statistical analyses, $p<0.05$ was considered to be significant.

Results

The study population comprised a total of 52 patients, 32 being female (61.5%) and 20 being male (38.5%). The age range of the patients was 19-89 years, with a median of 45.5 years. Among the patients, the number of attacks was 1 in 63.5% (*n*=33), was 2 in 15.4% (*n*=8), and was 3 in 21.2% (*n*=11). The type of AIHA was the warm type in all of the patients. Regarding the season during which attacks were experienced, it was determined to be winter in 26.9% (*n*=14), autumn in 17.3% (*n*=9), summer in 38.5% (*n*=20), and spring in 17.3% (*n*=9) of the patients.

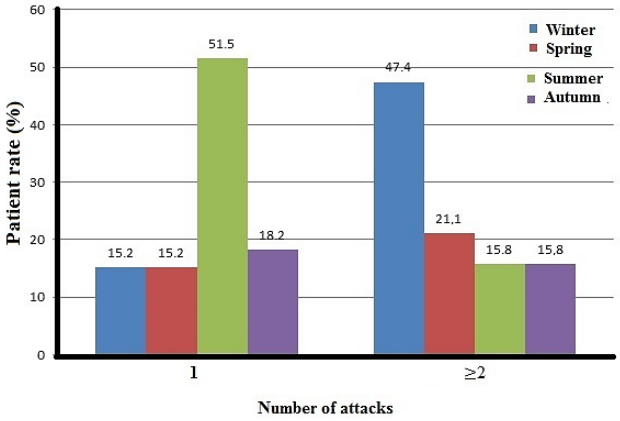

Figure-1. Distribution of number of attacks by seasons

Mean age, sex distribution, comorbidity distribution, blood group distribution, and Rh rates did not differ between the group with number of attacks of 2 or more and the group with number of attacks of 1. All of the patients were found to be receiving steroid treatments. Splenectomy rate and the ratio of the patients who received rituximab were determined to be higher among the patients with number of attacks of 2 or more ($p<0.001$ and $p<0.001$, respectively). Although the ratio of those who received intravenous immunoglobulin was higher in the group with number of attacks of 2 or more, this showed no statistical significance ($p>0.05$)(Table-1). The incidence rate of having an attack during the winter season was higher in the patient group with number of attacks of 2 or more compared to the other attack group; in the patient group with number of attacks of 1, however, the incidence rate of having an attack during the summer and autumn was determined to be higher (p=0.03)(Figure-1).

Table-1. Distribution of clinical-demographic characteristics according to the number of attacks

Variables	Number of Attacks		P Value
	1 (n: 33)	≥2 (n: 19)	
Age (year)	44(19-89)	48(27-65)	0.747
Gender (n%)			
▪ Female	21(63.6)	11(57.9)	0.771
▪ Male	12(36.4)	8(42.1)	
Comorbidity (n%)			
▪ Diabetes Mellitus	6(18.2)	4(21.1)	0.999
▪ Hypertension	9(27.3)	4(21.1)	0.868
▪ CAD	3(9.1)	2(10.5)	0.999
▪ Respiratory diseases	7(21.2)	2(10.5)	0.548
Blood group (n%)			
▪ 0	13(39.4)	6(31.6)	0.828
▪ A	12(36.4)	6(31.6)	
▪ B	5(15.2)	4(21.1)	
▪ AB	3(9.1)	3(15.8)	
Rh Antigen (n%)			
▪ Pozitive	30(90.9)	16(84.2)	0.656
▪ Negative	3(9.1)	3(15.8)	
Treatment option (n%)			
▪ Steroid	33(100)	19(100)	-
▪ Splenectomy	1(3)	11(57.9)	<0.001*
▪ IVIG	1(3)	2(10.5)	0.618
▪ Rituximab	1(3)	10(52.6)	<0.001*
▪ Plasmapheresis	2(6.1)	1(5.3)	0.999
Season (n%)			
▪ Winter	5(15.2)	9(47.4)	0.030*
▪ Autumn	6(18.2)	3(15.8)	
▪ Summer	17(51.5)	3(15.8)	
▪ Spring	5(15.2)	4(21.1)	

Abbreviations: CAD: Coronary artery disease Normally distributed numerical variables were shown as mean±standard deviation. Numerical variables that do not show normal distribution were shown with median (min-max). Categorical variables were shown as number (%). * p<0.05 shows statistically significance.

No significant difference was determined between patients' laboratory findings and the attack groups (Table-2). Median splenomegaly rate was determined to be higher among patients with number of attacks of 2 or more compared to the patients with number of attacks of 1 (p=0.047). No significant difference was determined between other hematological findings and number of attacks (Table-3). No significant correlation was determined between number of attacks and age and laboratory findings (Table-4).

Table-2. Distribution of laboratory findings according to the number of attacks

Variables	Number of Attacks		P Value
	1 (n: 33)	≥2 (n: 19)	
ESR (mm/h)	8(2-118)	5(1-87)	0.422
CRP (mg/dL)	5(1-107)	4(2-235)	0.334
Hemoglobin (g/dL)	6.6±1.5	6.5±1.3	0.874
Hemotocrit (5)	19.7±4.9	19.3±4.8	0.775
MCV (FL)	101.1±20.9	100.2±27	0.890
MCHC (%)	33.5±4.8	33.1±4.3	0.781
WBC (10^3µ/L)	7000(2800-43000)	8900(2700-24700)	0.615
Neutrophile (10^3µ/L)	5300(2000-31300)	5500(1100-22500)	0.790
Lymphocyte (10^3µ/L)	1800(400-14000)	1600(300-4300)	0.342
Monocyte (10^3µ/L)	400(100-6200)	500(0-1700)	0.871
Eosinophils (10^3µ/L)	0(0-600)	100(0-900)	0.393
Basophils (10^3µ/L)	0(0-300)	0(0-200)	0.855
Platelet (10^3µ/L)	244(98-611)	202(70-685)	0.704
MPV (FL)	8.4±1.7	8.2±1.5	0.723
RDW (%)	22.3±4.8	20.2±4.1	0.115
Reticulocyte (%)	4.3(2.3-16.8)	4.3(1.8-13.1)	0.662
Total bilirubin (mg/dL)	4.5(0.7-16)	3.9(2.4-9)	0.537
Indirect bilirubin (mg/dL)	3.3(0.6-12.9)	3.1(1.8-7.5)	0.323
LDH ratio	2.3(0.9-9.8)	2.1(1.1-3.2)	0.171

Abbreviations: ESR: Eritrocyte sedimantation rate, CRP: C-reactive proteine, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, WBC: White blood cell, MPV: Mean platelet volüme, RDW: Red distribution width, LDH: Lactate dehydrogenase. Normally distributed numerical variables were shown as mean ± standard deviation. Numerical variables that do not show normal distribution were shown with median (min-max). * p <0.05 shows statistical significance.

Table-3. Distribution of the hematological findings of the patients according to the number of attacks

Variables	Number of Attacks		P Value
	1 (n: 33)	1 (n: 33)	
Direct Coombs			
▪ Pozitive	31(93.9)	18(94.7)	0.999
▪ Negative	2(6.1)	1(5.3)	
Indirect Coombs			
▪ Pozitive	32(97.0)	17(89.5)	0.285
▪ Negative	15(45.5)	5(26.3)	
Indirect Coombs-B			
▪ 1+	-	0(.0)	0.215
▪ 2+	5(15.2)	1(5.3)	
▪ 3+	6(18.2)	8(42.1)	
▪ 4+	7(21.2)	5(26.3)	
▪ Negative	15(45.5)	5(26.3)	
Indirect Coombs-I			
▪ 1+	2(6.1)	0(.0)	0.123
▪ 2+	5(15.2)	2(10.5)	
▪ 3+	4(12.1)	8(42.1)	
▪ 4+	6(18.2)	4(21.1)	
▪ Negative	16(48.5)	5(26.3)	
Indirect Coombs-U			
▪ 1+	1(3.0)	0(.0)	0.159
▪ 2+	6(18.2)	2(10.5)	
▪ 3+	5(15.2)	8(42.1)	
▪ 4+	5(15.2)	4(21.1)	
▪ Negative	16(48.5)	5(26.3)	
IgG			
▪ 1+	-	0(.0)	0.589
▪ 2+	2(6.1)	2(10.5)	
▪ 3+	8(24.2)	7(36.8)	
▪ 4+	20(60.6)	8(42.1)	
▪ Negative	3(9.1)	2(10.5)	
C_3			
▪ 1+	2(6.1)	1(5.3)	0.689
▪ 2+	2(6.1)	2(10.5)	
▪ 3+	4(12.1)	5(26.3)	
▪ 4+	7(21.2)	3(15.8)	
▪ Negative	18(54.5)	8(42.1)	
Haptoglobin	1.6(0.2-6.5)	2.6(0.1-5.8)	0.805
Splenomegaly	133.7±13.5	147.4±26.5	0.047*

Normally distributed variables were shown as mean ± standard deviation. Numerical variables that do not show normal distribution were shown with median (min-max). Categorical variables were shown as number (%). *p<0.05 shows statistical significance.

Table-4. Correlation between the number of attacks and age and laboratory findings

Variables	Number of attacks	
	r	p
Age	0.027	0.848
ESR	-0.104	0.461
CRP	-0.181	0.200
Hemoglobin	0.016	0.909
Hematocrit	-0.051	0.720
MCV	0.047	0.740
MCHC	0.005	0.971
WBC	-0.054	0.705
Neutrophil	-0.032	0.819
Lymphocyte	-0.117	0.408
Monocyte	0.020	0.890
Eosinophils	0.146	0.301
Basophils	0.039	0.782
Platelet	-0.008	0.954
MPV	-0.025	0.860
RDW	-0.215	0.127
Reticulocyte	0.054	0.705
Total bilirubin	-0.087	0.538
Indirect bilirubin	-0.121	0.392
LDH ratio	-0.137	0.331
Haptoglobin	0.024	0.935
Splenomegaly	0.255	0.068

Abbreviations: ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, WBC: White blood cell, MPV: Mean platelet volume, RDW: Red distribution width, LDH: Lactate dehydrogenase. Normally distributed numerical variables were shown as mean± standard deviation. Numerical variables that do not show normal distribution were shown with median (min-max). Categorical variables were shown as number (%). *p<0.05 shows statistical significance.

Discussion

Our objective in this retrospective study was to investigate the association of warm-type AIHA and its course with the seasons; this association had not been investigated previously. As the conclusion of our study, while the ratio of patients who had experienced only one AIHA attack was observed to increase during summer and autumn seasons, patients with more than 1 attack were determined to have their attacks arise most commonly during the winter season. Another obtained result was that the patients with more than one attack were resistant to steroid treatment and they were patients who needed splenectomy and rituximab treatment more commonly.

The first type of immune destruction of erythrocytes is cell-mediated and the second one is complement-mediated intravascular hemolysis. Cell-mediated immune destruction of antibody-coated erythrocytes is performed by macrophages and monocytes. These cells have a cell surface receptor for the Fc portion of IgG and have antigenic receptors presenting on active C_3. Cellular immune destruction takes place via these receptors. Neutrophils and lymphocytes have such receptors.

Macrophages have Fc receptors for IgG_1 and IgG_3 molecules. IgG-coated erythrocytes are destructed in this way and 70%-75% of the autoantibodies destructed in warm-type AIHA are IgG. Phagocytosis and antibody-mediated cytotoxicity are important Fc receptor-dependent modes of the important antibody-coated material. Two types of C_3 receptors have been identified in macrophages: CR_1 and CR_3. While adhesion of C_{3b}-coated erythrocytes takes place via the CR1 receptor, adhesion of CR_3 triggers phagocytosis. The main region for capturing and phagocytizing C_{3b}-coated erythrocytes is the liver. In warm-type AIHA, a complement-induced immuno globulin class is present on the erythrocyte membranes. When more than one class or subclass of immunoglobulins is present on the erythrocyte membrane, complement-mediated intravascular hemolysis occurs (6-9).

When we reviewed studies investigating seasonal association of autoimmune diseases, we observed that autoantibody levels were shown to be elevated during winter months in

autoimmune disease-associate type-1 diabetes mellitus patients. It was demonstrated that, in rheumatoid arthritis patients, relapses increased during the summer season in those patients with rheumatoid factor positivity. In Behçet's disease, activation of intestinal Behçet's disease was found to be increased during autumn and spring. In another study on idiopathic thrombocytopenic purpura (ITP), it was observed to be more common during autumn and spring months. In this study, we did not include patients with cold-type autoimmune diseases whose number of attacks would be more due to the cold weather of winter. Additionally, we excluded patients with another autoimmune disease, such as SLE, who were likely to experience an autoimmune hemolytic anemia attack due to exacerbation of the disease (16, 18, 21).

The fact that climate changes play an important role in the pathogenesis of auto immune diseases was mentioned above. In the pathogenesis of ITP, T cell-mediated immune mechanisms that allow formation of antibodies against the GPIIb/IIIa and GPIb/IX, which are thrombocyte surface antigens responsible for destruction of thrombocytes, were blamed. In T cell-associated mechanisms, impairment of the Th-1/Th2 ratio and oligoclonal T cell expansion are also responsible. The increased number of AIHA attacks during summer and autumn may be associated with increased allergenic pollens. These allergens may increase the destruction of erythrocytes by leading to complement activation via B or T cell-mediated immune regulation. This has been demonstrated in studies in which seasonal associations of these autoimmune diseases with allergic diseases were investigated (22-24).

In a study on SLE, it was shown that SLE findings increased during summer and autumn and autoantibody levels were elevated during these seasons. The severity of cellular immunity-associated destruction of erythrocytes depends mainly on the macrophage function. In SLE, reticuloendothelial function may be diminished by the clearing of immune complexes. Hypo complementemia is common in SLE and it leads to hemolysis via chronic activation of the complement pathway. DAT positivity may be due to accumulation of immune complexes on the erythrocyte surface. The spleen is important in clearing such coated cells. We thought that the increase in incidence of AIHA during summer and autumn may occur as a result of increased complement and macrophage activations, which may also cause activation of the other autoimmune diseases mentioned above (17, 18).

Viral infections may trigger warm-type AIHA; alterations on the erythrocyte membrane due to viral antigens, "auto"-antigens formed against the altered antigens, or cross-reactivity of antiviral antibodies with membrane antigens have been blamed. However, is formation of immune complexes between a virus and specific antibodies and secondary accumulation of these complexes on red blood cell surfaces, leading to immune destruction. The influenza virus has been blamed in the pathogenesis of ITP as a responsible agent for a long time, as it causes thrombocyte autoantibodies (25, 26).

Frequent exposure of the patients with more than one attack in our study to viral infectious agents during the winter season causes progressive inflammation and autoimmunity, leading to an increase in T cell response. Immune disorders that occur because of this increase in T cell response may explain why

patients experience more than one AIHA attack and why they are more resistant to treatment. This association was mentioned in another study on autoimmune diseases (27).

Collection of the patients from one region, being a single-center study, failure to test the genetic predisposition of the patients to allergens, and failure to detect infectious agents during attack periods are the limitations of our study.

Although seasonal association of other auto immune diseases has been revealed, this is the first study in which the seasonal association of warm-type AIHA is revealed. However, concerning disease, randomized, prospective, multi-center studies in which patients' genetic predisposition and auto antibody levels are determined are needed.

Conflict of Interests

The authors declare that they have no competing interests.

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