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AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA);

A HEMATOLOGIC PERSPECTIVE AT A TERTIARY CARE HOSPITAL.

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ABSTRACT… Objectives: Autoimmune hemolytic anemia (AIHA)- an immunological disease resulting from red cell hemolysis caused by circulating autoantibodies against antigens on red cell membrane. Positive direct antiglobulin test (DAT) always exist in association with AIHA and form basis for its serologic diagnosis. The objective of our study was to determine clinical presentation and etiological pattern in autoimmune hemolytic anemia at a tertiary care hospital. **Study Design:** Descriptive, cross-sectional study. **Setting:** Medical unit I of Liaquat University Hospital Jamshoro / Hyderabad. **Period:** 1st January 2010 to 30th June 2010. **Patients and Methods:** We enrolled 125 patients of either sex and ages from 13 to 81 years for evaluation of possible AIHA. We screened patients by performing direct and indirect antiglobulin tests (DAT and IAT) and cold agglutinin titre (CAT) levels. Pregnant women or those with history of blood transfusion in previous three months, DAT positive patients due to Rh and ABO incompatibilities in neonates and IAT positives cases in Rh-negative pregnant women were excluded. **Results:** We evaluated 125 patients who were DAT positive autoimmune hemolytic anemia. About 93(74.4%) were females and 32(25.6%) males with female to male ratio of 2.9:1. The mean age of our patients was SD ± 36.73 ± 9.32 years. Our patients commonly presented, generalized weakness in 33(26.4%), pallor of face and extremities in 22(17.6%) and breathlessness in 20(16%) respectively. On clinical examination, moderate to severe anemia was noted in 100(80%), splenomegaly in 40(32%), hepatosplenomegaly in 28 (22.4%) and no visceromegaly in 30(24%) of our cases. We found 35(28%) with primary and 90(72%) patients due to secondary causes of AIHA. The connective tissue disorders, renal failure and hematological disorders were common causes of secondary AIHA in this study. **Conclusion:** Our study showed females in their thirties presented with generalized weakness, pallor of face and extremities and breathlessness. Majority had secondary AIHA due to consecutive tissue disorders, renal failure and hematological disorders as underlying causes. Doctors must be cautious regarding whole blood transfusion as means for treating mild to moderate anemia.

Key words: Clinical presentation, etiological pattern, autoimmune hemolytic anemia (AIHA), direct antiglobulin test (DAT).

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INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is an acquired immune disorder characterized by production of antibodies that bind to surface of circulating erythrocytes leading to hemolysis and shortened red blood cell (RBC) life span with removal by reticuloendothelial system. The annual incidence of AIHA is 1-3 per 100,000 peoples in general population.[1] AIHA occurs more frequently in adults but not rare in pediatric population especially during early years of life and can develop following viral infections and vaccinations.[2] On etiological basis, they are typed as primary (Idiopathic) and secondary (due to underlying cause). The commonest type of AIHA is characterized by the presence of "warm" type of autoantibodies (IgG) which react optimally at 37ºC causing RBC destruction by tissue macrophages extravascularly.[3] Warm autoantibodies are responsible for upto 70% of AIHA cases.[4] In warm-antibody AIHA, IgG antibodies opsonize red blood cells and are mainly cleared in spleen being recognized by mononuclear phagocytic cell having Fc-receptors (extravascular hemolysis).[5]

The other two autoantibodies include "cold" agglutinins (IgM) and Donath-Landsteiner antibodies (IgG type). The hallmark of diagnosis of AIHA is a positive result of direct anti- globulin

test (DAT) in presence of hemolysis, which detect coating of immunoglobulin or components of complement on RBC surface and sometimes free antibody can be seen in serum (indirect anti-globulin test). On clinical examination, these patients present with variable features including a sudden onset of anemia, mild jaundice and splenomegaly. Although, the rate of hemolysis and hence clinical features depend mainly on the type of antibodies and their capacity to fix complements, yet underlying cause and demographics also play an important role.[3]

This study is important in our context as large number of anemic patients are managed by whole blood transfusion and hence it provides a tool for diagnosis (i.e to find out cause) and about future consequences. The objective of our study was to determine clinical presentation and etiological pattern in autoimmune hemolytic anemia at a tertiary care hospital.

Material and Methods

This descriptive, cross-sectional study was conducted at Medial unit I of Liaquat University Hospital Jamshoro/Hyderabad from 1st January 2010 to 30th June 2010. All participants gave informed and written consent and study was approved by institutional ethical committee.

We enrolled 125 patients of either sex and ages from 13 to 81 years for evaluation of possible autoimmune hemolytic anemia by laboratory screening test. We also noted demographic characteristics, presenting complaints of patients and performed clinical examination for systemic signs of the disease. Our patients were screened by performing direct and indirect anti- globulin test (DAT and IAT) and cold-agglutinin titer (CAT) levels. All DAT positive patients were included in this study. For DAT and IAT, we used gel card technique utilizing Diamed id cards with polyspecific antihuman globulin. We correlated different laboratory parameters including hemoglobin level, total and differential leukocyte counts, reticulocyte count and peripheral blood picture results. Other laboratory investigations were carried out when needed like serum indirect bilirubin, lactate dehydrogenase, heptoglobin levels, bone marrow examination, ANA profile, RA factor etc. Pregnant women or those with history of blood transfusion in previous three months, DAT positive patients due to Rh and ABO incompatibilities in neonates and IAT positive cases in Rh-negative pregnant women were excluded from study.

The database was analyzed and compiled in excel sheet and only percentage calculations were applied as our study was observational.

RESULTS

We evaluated 125 patients during this study. The age of our patients ranged from 13-81 years (mean age SD 36.73 ± 9.32 years). About 93 (74.4%) were females and 32 (25.6%) males with female to male ratio of 2.9:1. Our patients commonly presented, generalized weakness in 33 (26.4%), pallor of face and extremities in 22 (17.6%) and breathlessness in 20 (16%) respectively. The joint pains, fever and bleeding from gums and body orifices were commonly attributed to secondary causes of autoimmune hemolytic anemias. On clinical examination, moderate to severe anemia was noted in 100 (80%), splenomegaly in 40 (32%), hepatosplenomegaly in 28 (22.4%) and no visceromegaly in 30 (24.0%) of our cases. These findings are shown in tables-I and II. Reticulocytosis, although much more common in primary (65%) than secondary (20%) causes of autoimmune hemolytic anemia, was evident in 85% of our patients. However, thrombocytopenia (platelet counts < 1.0 x 105/ μl) was more often evident in secondary (32%) than primary (21%) cause of AIHA. Peripheral blood smear examination of our patients with AIHA revealed immature, nucleated RBCs with associated clumping, fragmentation of RBCs and polychromasia. This evidence of chronic hemolysis was more often seen in primary (45%) than secondary (25%) AIHA. Serological findings showed that 40% of primary AIHA were positive for both DAT and IAT indicating elevated titres of autoantibodies in their blood. Majority of DAT positive cases were due to secondary (80%) than primary (57.14%) cause of AIHA. Only one patient had cold agglutinin titre (CAT) elevated in this study. This is shown in table-III.

S.No	History	Primary	Secondary
1.	Generalized Weakness	12	21
2.	Pallor of face and extremities	8	14
3.	Breathlessness	7	13
4.	Fever	4	13
5.	Joint pain	1	17
6.	Abdominal pain	1	4
7.	Bleeding from gums and body orifices	2	8
	Total	35	90
Clinical Examination			
8.	Splenomegaly	18	22
9.	Hepatosplenomegaly	10	18
10.	Hepatomegaly	3	11
11.	Lymphadenopathy	3	10
12.	No visceromegaly	1	29
	Total	35	90

Table-I. Clinical Presentation of Patients with Autoimmune Hemolytic Anemia (N=125)

S.No	Hemoglobin Level (g/dl)	Primary	Secondary
1.	Severe (0-7g/dl)	15	32
2.	Moderate(7-10g/dl)	15	38
3.	Mild(10-12g/dl)	4	15
4.	>12g/dl	1	5
	Total	35	90

Table-II. Degree of anemia on clinical presentation (n=125)

S.No	Antiglobulin Test	Primary	Secondary
1.	DAT	20	72
2.	DAT + IAT	14	18
3.	DAT + CAT	1	0
	Total	35	90

DAT: Direct antiglobulin test
IAT: Indirect antiglobulin test
CAT: Cold agglutinium titre

Table-III. Serological finding in AIHA (n=125)

Our study found 35 (28%) patients with primary and 90 (72%) due to secondary causes of AIHA. The connective tissue disorders, renal failure, hematological disorders and malignancies were common causes of secondary AIHA in this study. This is shown in table-IV.

S.NO	CAUSES	No. of patients	Percentage
A. Primary (Idiopathic)		35	28%
B. Secondary		90	72%
1B.	Connective tissue disorders	31	34.4%
2B.	Renal failure	17	18.8%
3B.	Hematological disorders	13	14.4%
4B.	Hematological malignancies	11	12.2%
5B.	Drug induced	8	8.88%
6B.	Tuberculosis	3	3.33%
7B.	HIV infection	1	1.11%
8B.	Miscellaneous causes	6	6.66%

Table-IV. Causes of autoimmune hemolytic anemia in our patients (n=125)

DISCUSSION

We discovered varied clinical presentation, etiology and hematological spectrum in 125 cases of AIHA depending upon positive direct antiglobulin test in a sample population of Sindh. Auto- immune hemolytic anemia (AIHA) is an example of extravascular hemolysis because red blood cells are destroyed in spleen and other reticuloendothelial tissues.6 AIHA can be due to warm or cold autoantibody and rarely mixed types, which can be detected by direct coombs test or direct antiglobulin test.[7,8] AIHA is slightly more likely to occur in females of middle aged than in males. In our study, females (74.4%) commonly affected by AIHA and their mean age was SD 36.73 ± 9.32. This is quite similar to results of study by Vanamala Alwar et al9 who also showed female predominance in their sample of Indian population. We found generalized weakness (26.4%), pallor of face and extremities (17.6%) and breathlessness (16%) as common presenting symptoms in our patients. Study by Vanamala Alwar et al9 showed major symptoms of anemia like fatigue and breathlessness in 36%

of their patient which is comparable to our results. Similarly, Choudhry et al10 studied 21 cases of AIHA and common presentations were pallor (89%), jaundice (43%) and fever (38%). However, sample size of their study was very limited. Majority of our patients (80%) had moderate to severe anemia, comparable to results of study by Vanamala Alwar et al9 who found moderate to severe anemia in 89.71% of their cases.

The prominent physical signs noted in this study were splenomegaly (32%), hepatosplenomegaly (22.4%) and no visceromegaly (24%). They were comparable to study by Vanamala Alwar et al[9] who found hepatomegaly (31.42%), splenomegaly (26.28%) and no visceromegaly (34.85%). This may be due to larger sample size of their study. The major cause of AIHA in our study was secondary (72%) diseases, while (28%) had primary etiology. The connective tissue disorders (34.4%), renal failure (18.8%), hematological disorders (14.4%) and hematological malignancies (12.2%) were common secondary etiologies. This is comparable by study of Vanamala Alwar etal9 who found secondary diseases (77.14%), while (22.85%) had primary etiology for AIHA. Similarly, connective tissue disorders (46.6%), renal failure (14.07%) and hematological malignancies (10.37%) were significant causes in their study. In our study, 99.2% had warm-antibody type of AIHA while only 0.8% showed cold agglutinins in their serum. These results were quite similar to study by Vanamala Alwar etal9 who showed warm-antibody titres in 99%, while cold- agglutinin in 1% of their cases. Similarly, connective tissue disorders was commonest cause and hematological malignancies were rare secondary cause of AIHA in their study. However, Genty et al11 studied 83 cases and found 51% of warm-antibody titers secondary to non-Hodgkin's lymphoma and connective tissue disorders (14 cases each). They conclude that AIHA may point towards diagnosis of lymphomas and hence requiring detailed workup.

CONCLUSION

On conclusion, females in their third decade of life presented with generalized weakness, pallor of face and extremities and breathlessness. The common physical signs were splenomegaly and hepatosplenomegaly along moderate to severe anemia and reticulocytosis. Majority had secondary AIHA due to consecutive tissue disorders, renal failure and hematological disorders as underlying causes. Doctors must be cautious regarding whole blood transfusion as means for treating mild to moderate anemia.

RECOMMENDATION

This study provide an open message and recommendation to all healthcare profession personnel that:

- Avoid habitual treatment via blood transfusion to patients presenting with mild to moderate anemia.
- Try to probe into underlying etiology of anemia so that appropriate treatment can be initiated as early as possible.
- Avoid injudicious use of drugs causing or leading to anemia.

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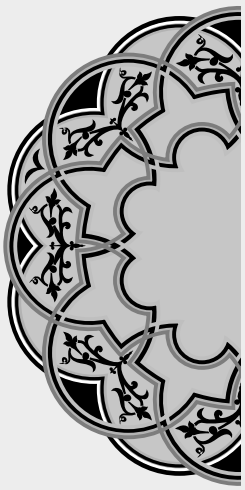

"If you wait until you're ready,
you'll be waiting the rest of your life."

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
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2	Dr. Mona Humaira	Literafare review and data collection	
3	Dr. Ghulam Nabi Pathan	statistical analysis	
4	Dr. Mohammad Adnan Bawany	Date collection and referewing	