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CAUSES OF AUTOIMMUNE HEMOLYTIC ANEMIA AND ITS CLINICAL PRESENTATION.

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ABSTRACT… Objectives: To evaluate various causes of autoimmune hemolytic anemia and its presenting signs and symptoms. **Study Design:** Cross sectional study. **Setting:** Fatima Jinnah Medical College Lahore. **Period:** November 2018 to April 2019. **Material & Methods:** In this study 90 cases were included having age range of 14-75 years with mean age of 46.5 year with the possibility of autoimmune hemolytic anemia (AIHA). Screening test used for evaluating AIHAin this study include Direct and Indirect Antiglobulin Tests and Cold Agglutinin Titer (CAT). All relevant data was documented properly. **Results:** Total 90 cases were included in the study comprising on 71% female and 29% male cases. 22.2% cases were having primary and 77.8% were having secondary autoimmune hemolytic anemia. Most common presenting complaint was generalized body weakness in 25(27.7%) cases and on examination most common finding was splenomegaly in 30(33.3%) cases. Hemoglobin was less than 8g/dl in 28(31%) cases. Direct Antiglobulin test was positive in 64(71%) cases, DAT and IATboth were found to be positive in 22(24.4%) cases and DAT and CAT both found positive in 4(4.4%) cases. Blood transfusion was done in 28% cases having severe anemia. Most common cause of autoimmune hemolytic anemia found among study group patients was connective tissue disorder in 25(27.8%) cases. P-value less than 0.05 were considered significant and more than 0.05 was non-significant. **Conclusion:** In our study autoimmune hemolytic anemia was mostly found in female population with most common presentation of generalized body weakness, pallor of hands, hepatosplenomegaly and severe anemia. Most common cause found of AIHA was connective tissue disorders.

Key words: Autoimmune Hemolytic Anemia, Direct Antiglobulin Test, Indirect Antiglobulin Test, Cold Agglutinin Titer, Causes of Anemia.

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INTRODUCTION

Autoimmune hemolytic anemia is a disorder in which a specific type of antibodies is produced in the body which attaches to the surface of RBCs and cause their hemolysis early leading to development of anemia. Direct Antiglobulin Test is used to diagnose it. It is a rare type of disease. Still here are no proper guidelines for its treatment based on evidence.[1] According to a study DAT found negative in 3-11% of cases hence requiring any other specialized test to diagnose this disease.[2] All over the world its incidence is 1-3% in 100,000 populations.[3] Diagnosis of AIHA is made on the basis of clinical signs symptoms and laboratory findings such as anemia, increased serum level of bilirubin (indirect), low serum level of Haptoglobin and elevated serum Lactate dehydrogenase level. There is positive comb test (DAT test). In making diagnosis of AIHA we should rule out its hereditary and other causes as well.[4] AIHA is of two types on the basis of etiology primary and secondary. Primary AIHA is due to idiopathic causes and secondary AIHA is due to some underlying cause. Steroids play major role in the treatment of AIHA.[5,6] In such patients warm antibodies (IgG) are present in the blood which attach to RBCs surface and cause their opsonization. Other antibodies present are cold agglutinin (IgM) and Donath-Landsteiner antibodies (a type of IgG). Direct Antiglobulin Test detects antibodies on the surface of RBCs during hemolysis while Indirect Antiglobulin Test

detects free antibodies in the blood. This study is very important because many patients present with anemia and they are transfused with whole blood frequently not knowing the real cause of anemia. This study helps in making diagnosis of the patients having AIHA and helps in finding its cause as well. Our purpose of study was to determine findings in patients having AIHA presenting to a tertiary care hospital.

MATERIALS AND METHODS

This is a cross sectional study of descriptive type, conducted in Fatima Jinnah Medical College Lahore. Study was started in November 2018 and completed in April 2019 comprising on total duration of 6 months.

All cases in study group gave written consent. Permission was taken from ethical committee of the institution as well. We included 90 cases in this study which were reported in pathology department for evaluation of autoimmune hemolytic anemia. A proforma was designed in which data of the patients was documented such as age, sex, demographic data, presenting signs and symptoms, positive findings in history and physical examination. These cases were screened for AIHA by Direct Antiglobulin Test, Indirect Antiglobulin Test and Cold Agglutinin Titer. An inclusion and exclusion criteria was designed according to which all those cases were included in this study which showed positive Direct Antiglobulin Test. Pregnant ladies, history of blood transfusion in previous three months or patients having RH-ABO incompatibility in newborns also show DAT positive but they were excluded from this study. In DAT, gel card technique was used by DiaMedID cards with polyspecific antihuman globulin. Parameters from different pathological laboratories were correlated such as hemoglobin level, reticulocyte count, peripheral blood morphology, total leucocyte count and differential leucocyte count. Further investigations of cases included serum lactate dehydrogenase level, Haptoglobin level, serum indirect bilirubin level, serum RA factor, ANA level, moreover renal and liver function tests were also done for evaluating any complication or organ failure.

RESULTS

Total 90 cases were included in the study comprising on 64(71%) female and 26(29%) male cases. Primary AIHA was found in 20(22.2%) cases and secondary AIHA was found in 70(77.8%) cases. Presenting complaints of patients with primary AIHA included generalized weakness in 7(35%) cases, pallor of face and extremities 4(20%), dyspnea 3(15%), fever 2(10%), joint pain and abdominal pain in 1(5%) and 2(10%) cases respectively. Frequency of same complaints in cases with secondary AIHA were as generalized weakness in 18(25.7%), pallor in 10(14.3%), breathlessness 11(15.7), fever 9(12.8%), joint and abdominal pain in 12(17.14%) and 3(4.3%) cases respectively.

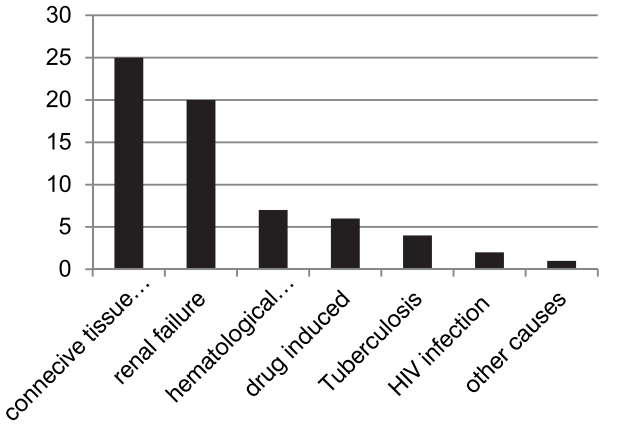

Figure-1. Causes of AIHA among patients in study group (N=90)

Primary AIHA has idiopathic cause. Causes of secondary AIHA included connective tissue disorders in 25(27.8%), renal failure in 20(22.2%), hematological disorders in 7(7.8%), hematological malignancies in 5(5.6%), drug induced AIHA in 6(6.7%), tuberculosis was found as a cause of AIHA in 4(4.4%), HIV infection in 2(2.2%) and miscellaneous causes found in one case.

On physical examination in patients with primary AIHA, splenomegaly was found in 10(50%), hepatosplenomegaly in 4(20%), only hepatomegaly in 3(10%) cases, lymphadenopathy in 1(10%) cases and no visceromegaly at all in 2(20%) cases. Findings on physical examination in patients with secondary AIHA noticed were: splenomegaly alone in 20(28.5%) cases,

hepatosplenomegaly in 15(21.5%), hepatomegaly alone in 8(11.4%) cases, lymphadenopathy in 9(12.9%) and no visceromegaly found in 18(25.7%) cases.

Patients with primary AIHA were having severe anemia (HB less than 7g/dl) in 8(40%) cases, moderate anemia (HB 7-10 g/dl) in 6(30%) cases and mild anemia (HB 10-12g/dl) was found in just one case. Similarly in patients group with secondary AIHA severe anemia was found in 20(28.6%) cases, moderate anemia in 35(50%) cases and mild anemia in 9(12.8%) cases.

Presenting Complaints	Primary AIHA (n=20)		Secondary AIHA (n=70)		P-Value
	N	Percentage (N/20)	N	Percentage (N/70)	0.152
Generalized body weakness	7	35%	18	25.7%	0.073
Fever	2	10%	9	12.8%	0.114
Pallor of face	4	20%	10	14.3%	0.169
Joint pain	1	5%	12	17.1%	0.046
Abdominal Pain	2	10%	3	4.3%	0.518
Bleeding from Gums and body orifices	1	5%	7	10%	0.352
Breathlessness	3	15%	11	15.7%	0.071

Table-I. Presenting complaints of patients in study group having Autoimmune Hemolytic anemia

Antiglobulin Test	Primary AIHA		Secondary AIHA		P-Value
	N	Percentage(N/20)	N	Percentage(N/70)	
DAT	11	55%	53	75.7%	0.155
DAT+IAT	6	30%	16	22.8%	0.732
DAT+CAT	3	15%	1	1.4%	0.084
Total	20	22.2%	70	77.8%	

Table-II. Serological results in AIHA (n=90)

Serological findings in patients with primary AIHA were positive DAT (Direct Antiglobulin Test) in 11(55%) cases, DAT and IAT (Indirect Antiglobulin Test) positive in 6(30%) cases and DAT and CAT (cold agglutinin test) both positive in 3(15%) cases while serological results in patients with secondary AIHA were positive DAT in 53(75.7%) cases, DAT and IAT positive in 16(22.8%) cases and DAT and CAT positive in 1(1.4%) case.

DISCUSSION

In this study we determined various signs and symptoms and laboratory findings in patients presenting to a tertiary care setup having autoimmune hemolytic anemia. Total 90 cases were studied. In AIHA RBCS are destroyed by auto antibodies leading to development of anemia. According to a study conducted in Croatia on 56 patients, 25% were having primary AIHA and 75% were having secondary causes of anemia. These results are very close as compared to our study in which 22% cases were having primary and 78% were having secondary AIHA.[7] Few studies have shown that flow cytometry is more sensitive to DAT and can detect low quantity of antibodies in the blood and can help in diagnosis AIHA. DAT many times give false negative results as it can't detect low quantity of immunoglobulin and diagnosis is missed so in this regard flow cytometry is suitable investigation.[8] There are various secondary causes of AIHA and tumors are one of them. Surgical excision of tumors can treat anemia and in these cases medical treatment has no significant role.[9] Other causes of secondary AIHA include connective tissue disorders, renal failure, hematological disorders, hematological malignancies, drug induced, associated with other infectious diseases such as tuberculosis and HIV infection. Tuberculosis causes increased production of IgG and IgM

antibodies and can cause Warm agglutinin, Cold agglutinin or mixed type AIHA.[10] Steroids therapy is very effective in AIHA and few studies have shown that steroid reduce hemolysis and hence improves hemoglobin without transfusion of blood while transfusion is needed in severe anemia. Intravenous use of immunoglobulins also show good results according to some studies and this can be used another treatment option along with steroid use. Steroids are effective against warm antibodies AIHA while in cold antibodies AIHA its role is very limited and in these cases intravenous immunoglobulin play significant role.[11,12] In our study primary AIHA was found in 22% cases and secondary AIHA was found in 77% cases that is comparable to a study in which 46% cases were having primary AIHA. This percentage is much high than our study but that can be change due to demographic and ethnicity difference.[13,14] According to a study conducted in a tertiary care hospital of France, anemia was present in 83% cases and breathlessness and chest pain was presenting complaint in 9% cases, need for blood transfusion was in 52% cases with primary AIHA and 72% cases with secondary AIHA. These results are comparable to our study results with breathlessness in 15% cases and moderate to severe anemia was present in 69% cases, transfusion needed in 40% of cases with primary AIHA and 28.5% cases with secondary AIHA.[15,16] Another study reported weakness and fatigue in all cases of study group, dyspnea in 53%, jaundice in 41%, abdominal pain in 41%, pallor in 86% and hepatosplenomegaly in 44.2% cases. In our study abdominal pain was present in 5.5%, splenomegaly was found in 33.3% and hepatomegaly was found in 12.2% cases.

CONCLUSION

Autoimmune hemolytic anemia is a rare disease and is frequently neglected or misdiagnosed. Mostly found in female population with most common clinical presentation of generalized body weakness, pallor and on examination hepatosplenomegaly is common finding. Secondary AIHA is more common than Primary AIHA. Steroids therapy play major role in initial treatment of it with excellent outcomes. Direct Antiglobulin Test is very helpful in diagnosing the patients with AIHA. Patients with primary AIHA are more anemic than the cases with secondary type of anemia.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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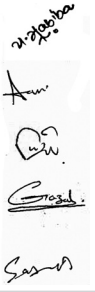
1	Umme Habiba	Topic Selection and data collection.	
2	Anam Ilyas	Data collection.	
3	Farwa Sijjeel	Data composing.	
4	Ghazala Tabassum	Data collection.	
5	Sabeen Fatima	Found additional resources of information.	