AFRICAN JOURNAL OF MEDICINE
and medical sciences

VOLUME 31, NUMBER 2 JUNE 2002

EDITOR:
B. O. OSOTIMEHIN

ASSISTANT EDITOR:
A. O. UWAIFO

ISSN 1116 — 4077

Afr. J. Med. med. Sci. (2002) 31, 97-100

Autoimmune haemolytic anaemia: pattern of presentation and management outcome in a Nigerian population: a ten-year experience

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Summary

Autoimmune haemolytic anaemia (AHA) is one of the commonest autoimmune disorders of man. It is characterised by the binding of anti-erythrocyte autoantibodies to red blood cells and destruction of the coated cells in the reticulo-endothelial system. Autoimmune disorders are said to be rare in indigenous African population, probably due to the widespread infectious diseases, which impair host's T-cell immunity. This study is therefore aimed at investigating the pattern of presentation and management outcome of patients with AHA seen over a period of 10 years (June 1988 to May 1998) at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife. We retrospectively analysed the records of patients with respect to the clinical, haematological, biochemical and serological features of AHA seen within the study period. Diagnosis was based on laboratory features of haemolytic anaemia and/or a positive direct anti-human globulin (Coombs') test after excluding other causes of haemolytic anaemia. Treatment protocol and outcome were noted in all cases. We identified 13 patients with AHA (7 females, 6 males) aged 6 – 70 (median, 42) years. Six (42%) had secondary AHA and the remaining 8 presented with primary (idiopathic) AHA. Laboratory evidence of haemolysis (bone marrow erythroid hyperplasia and hyperbilirubinaemia) was found in all cases, while the direct Coomb's test was positive in 10 (76.9%) cases. All the patients had moderate-severe anaemia within the course of the disease, requiring blood transfusion. Remission was induced with prednisolone in all except three cases with secondary AHA who died of the primary disease before AHA could be controlled. Follow-up period post-remission ranged between 1 and 78 months. However, 2 (20%) are still being followed-up till the time of this report. This study agrees with the view that autoimmune disorders are not common in Nigerians, as documented for other Africans. It also shows that steroid therapy (prednisolone) is quite effective, especially, in idiopathic AHA, and that red cell transfusion could be useful in life-threatening anaemia.

Keywords: *AHA, pattern of presentation, management outcome*

Résumé

L'anémie haemolytique d'auto-immune est un désordre le plus commun chez les êtres humains. C'est caractérisé par des anticorps, anti-erythrocyte aux globales rouges et la destruction des cellules recouvertes dans le système réticulo-endothélial. Les désordres auto immun sont rares parmi la population africaine indigène, peut être dû au fait des maladies contagieuses courantes qui est un obstacle à l'immunité de cellule-T. Cette étude est donc visé à examiner la manière de la présentation et le résultat de gestion des malades ayant AHA et examinés pendant une période de 10 ans (juin 1988 à mai 1998) au centre hospitalier universitaire d'Obafemi Awolowo, Ile-Ife. Nous avons analysé rétrospectivement les rapports des malades à ce qui concerne les caractéristique clinique, haemotologique, biochimique et serologique d'AHA trouvés pendant la période d'étude. Le diagnose est basé sur des caractéristiques d'anémie haemolytique et/ou un examen de globuline ante-humain directe positive (Cooms) après avoir exclus d'autres causes d'anémie haemolytique. Le protocole de traitement et les résultats ont été noté dans tous les cas. 13 malades ayant AHA étaient identifiés (7 femmes et 6 hommes âgé de 6 à 70 (médecin 42) ans six (42%) avaient AHA primaire (idiopathique). Une prévue laboratoire d'hémolyse (l'hyperplasie erythroide de la moelle osseuse et l'hyperbiliru binaemia) était découvert dans tous les cas, tandis que l'essai de Coomb direct était positif dans 10 (76,9%) cas. Tous les malades avaient l'anémie à proportion modéré sévère lors de la maladie qui a nécessité une transfusion du sang. La rémission était provoqué avec prédnisolone dans tous mais trois cas ayant l'AHA secondaire qui étaient mort de la maladie primaire avant que l'AHA soit contrôlé. La période de suivi post-rémission était entre 1 à 78 mois. Pourtant, une suivie de 2 (20%) est toujours en cours même jusqu'au temps de ce rapport. Cette étude confirme le point de vue que les désordres auto-immune ne sont pas communs chez les Nigérians comme noté pour les autres africains. Il montre aussi que le thérapie de stéroïde (prednisolone) est tellement effective en particulier au cas de l'idiopathique d'AHA et que la transfusion de globule rouge pourrait être utile pour le traitement d'anémie mortel.

Introduction

Autoimmune disease results from immune response to self-antigens resulting in damage to the target organs [1]. In autoimmune haemolytic anaemia (AHA), autoantibodies are produced against red blood cells, which cause a shortened survival of the cells. The triggering factor in most cases of autoimmune disorders is unknown. Some cases are, however, associated with some disorders or drugs with greater frequency than can be explained by chance alone. This group is referred to as secondary AHA. In view of the general belief that autoimmune disorders are generally rare in indigenous Africans [2,3] due to widespread infections, which impair host's T-cell immunity [4], we retrospectively analyzed the clinical and laboratory features, as well as management outcome of confirmed cases of AHA seen over a period of 10 years in our institution to determine the prevalence and the characteristics of this seemingly rare disorder in this environment.

Materials and methods

A ten-year retrospective study of cases of AHA seen at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife between June 1988 and May 1998 was carried out. The clinical presentation, and the results of serological, haematological and biochemical investigations were noted. Patients with sickle cell disorders (SCD), and those with history suggestive of glucose-6-phosphate dehydrogenase (G6PD) deficiency and paroxysmal nocturnal haemoglobinuria (PNH) without any proven evidence of concomitant AHA (e.g., positive DAT) were excluded.

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Specifically, the following were analyzed in detail: demographic data, clinical manifestations and drug history, as well as history of disorders known to be associated with AHA. In addition, all the patients underwent the following investigations at presentation: complete blood count, direct and indirect Coombs' test [5], haemoglobin electrophoresis, bone marrow as
piration, as well as Ham's test [5]. Serum bilirubin and lupus erythematosus (LE) cell test were also checked.

Diagnosis was confirmed in patients with anaemia associated with positive direct Coomb's test (DAT), laboratory evidence of haemolysis, including raised serum bilirubin, bone marrow erythroid hyperplasia and reticulocytosis. Also included were patients with anaemia, laboratory evidence of haemolysis but with negative DAT but no evidence of SCD, PNH and G6PD deficiency, such cases are labeled Coomb's negative AHA.

Financial constraints would not permit us to identify the immunoglobulin class of the anti-erythrocyte antibody (ies) present in patients with positive direct antihuman globulin test. Since we practice in a tropical environment, we also did not check for the presence of cold agglutinin in any of the patients. Consequently, all cases were considered warm AHA.

All confirmed cases of AHA had prednisolone (1mg/kg/day). In addition, those with primary disease, such as malignant lymphoma, had appropriate therapy. Antacid and H_2-antagonist were also added to prevent steroid-induced gastric ulceration. Some of the patients had emergency packed red cells transfusion at presentation, however, almost all the patients were transfused with packed parked red cells in the course of therapy. The indication in each case was severe life-threatening anaemia. Response was assessed with weekly complete blood count and serum bilirubin, and monthly evaluation of DAT. Patients who are no longer anaemic and with or without negative DAT, were considered to be in remission and had their steroid adjusted to the minimum dosage required to prevent haemolysis. Patients with persistent positive DAT and with no significant rise in haemoglobin value were considered as "treatment failures". Patients in remission were followed-up every four weeks at the Haematology outpatient clinic. Long remitters had their steroid discontinued, however, none of the patients was ever discharged from follow up.

Results

Clinical presentation

Of the 400,483 new patients seen in our institution during the period under review, 13 (0.003%) were confirmed as having AHA. There were 6 males and 7 females with a male to female ratio of approximately 1:1. The median age at presentation was 42 years (range: 6-70 years). Period of illness before presentation ranged from < 1 to 52 weeks. None of the patients admitted having been exposed to α-methyldopa or mefenamic acid. Six of the patients, however, were confirmed to have primary disease: 4 had lymphoid malignancy, 1 had osteogenic sarcoma and the 6th had concomitant systemic lupus erythematosus (SLE) (Table 1). Evidence of systemic infection was found in 11 (84.9%) patients, while 9 (69.2%) others had clinical evidence of haemolysis at presentation (jaundice and/or haemoglobinuria) (Table 2). Although splenomegaly was found in 6 (46%) patients, massive splenomegaly (spleen ≥ 10cm) was found only in cases with neoplasm.

Laboratory findings

At presentation, moderate-severe anaemia was recorded in all patients, with haematocrit of less than 30%, while 7 (53.9%) patients also had thrombocytopaenia (platelets of less than 90 x 10^9/L (Table 3). The laboratory evidences of haemolysis found included reticulocytosis, bone marrow erythroid hyperplasia and hyperbilirubinaemia. The distribution of ABO and Rhesus blood groups, was not significantly different from the general population. Direct antihuman globulin test (DAT) was positive in 10 (76.9%) patients. Other serological tests also showed one patient to be positive for lupus erythematosus (LE) cell and another for hepatitis B surface antigen (HbsAg).

Table 1: Aetiological classification and serological findings

AHA	COOMBS' Positive	COOMBS' Negative
1. Idiopathic	4	3
2. Secondary		
a. Neoplasm		
- Hodgkin diseae	2	
- Non-Hodgkin lymphoma	1	-
- Multiple myeloma	1	-
- Osteogenic sarcoma	1	-
b. Collagen disease		
- SLE	1	-

Table 1 shows the distribution of the 13 cases based on aetiology and serological findings. Seven (53.8%) patients presented with idiopathic AHA and 6(46.2%) had associated primary disease.

Management outcome

Period of active therapy ranged between 1 and 5 weeks (Table 4) with clinical response recorded in 76.9% of the treated patients. Of the 10 patients that were followed up for various lengths of time (<1-604 weeks), only two are still being followed-up.

The association of a primary disease represented the main cause of mortality, as 3(50%) of such patients died within three weeks of diagnosis, two other patients with secondary AHA were lost to follow-up within 4 and 14 weeks of diagnosis, respectively. The last is, however, still being followed-up till date. This particular patient, the longest survivor, has had her steroids discontinued on and off. All patients with primary AHA remitted within 1-4 weeks of steroid therapy, though the majority of them later stopped attending clinics.

Discussion

The hospital prevalence of symptomatic AHA in the period of study was 0.003%. T his is in support of the observation of the rarity of the disease [7,8], particularly in Africa [2,3]. The erythrocyte autoantibodies in AHA are responsible for the haemolysis through an immune process. This arises through an underlying defect in immune-regulation in the setting of disorders such as neoplasia, collagen diseases or other disorders that can cause disturbances in the immune system, leading to an aberrant immune response to self-antigen [9]. It is however, important to note that, though there are no obvious primary diseases that may lead to immune dysregulation in the 7 patients with idiopathic AHA, six of the group presented with fever, which could be of bacterial or viral origin. The theory of molecular mimicry [1], whereby an infectious agent with antigen that is immunologically similar to the host antigens but differs sufficiently to induce an immune response when presented to the host immune system may be true. The pathogen-specific immune response

Table 2: Clinical features at presentation

SN	AGE (Yrs)	SEX (M/F)	DSBP (Weeks)	A-Path.	Fever (+/-)	Jaundice (+/-)	Haemogl-obinuria	Spleen (cm)	Liver (cm)
1	6	M	1	-	+	+	+	4	6
2	18	F	5	-	+	+	+	-	3
3	15	M	20	-	+	+	+	3	4
4	20	M	10	HD IVB	+	+	+	16	4
5	27	F	2	SLE	-	-	+	-	-
6	37	M	6	HD IVB	+	+	-	-	4
7	42	M	12	NHL	+	+	-	14	-
8	43	F	8	MM	+	-	-	-	4
9	50	F	52	-	+	+	+	7	7
10	50	F	12	-	+	+	-	-	5
11	52	M	8	-	-	-	-	-	-
12	56	F	0.2	-	+	-	-	-	-
13	70	F	3	OS	-	+	+	10	16

DSBP - Duration of symptoms before presentation
HD IVB - Hodgkin disease stage IVB
NHL - Non-Hodgkin lymphoma
OS - Osteogenic sarcoma
M/F - Male/Female
A-Path - Associated secondary pathology
SLE - Systemic lupus erythematosus
MM - Multiple myeloma
x/- - Present/absent
cm - Centimeters below the costal margin

Table 3: Laboratory features at presentation

SN	PCV %	WBC x 109/L	Platelet x 109/L	DAT +/-	HbsAg +/-	LE +/-	Blood group	Bilirubin(umol/L) B1	B2
1	8	5.8	98	+	-	-	B pos	31	-
2.	11	3.8	20	+	-	-	O pos	36	31
3	13	8.7	239	+	+	-	O pos	29	-
4	18	3.2	132	+	-	-	AB pos	37	22
5	19	4.0	18	+	-	+	A pos	15	-
6	17	2.6	28	+	-	-	O pos	12	10
7	14	2.0	16	+	-	-	B pos	51	13
8	25	4.4	175	+	-	-	O pos	13	-
9	29	3.1	177	-	-	-	A pos	60	30
10	16	5.5	76	-	-	-	A pos	12	-
11	15	4.9	71	-	-	-	A pos	16	-
12	15	11.0	54	+	-	-	O neg	14	5
13	18	2.8	185	+	-	-	O pos	40	25

WBC - White blood cell counts
DAT - Direct antihuman globulin test
HbsAg - Hepatitis B surface antigen status
+/- Positive/Negative.
LE - Lupus erythematosus test
B1 - Total bilirubin
B2 - Conjugated bilirubin

that is generated can cross-react with the host's structures to cause disease. The implication of the postulate is that the majority of the cases of AHA usually labeled as idiopathic may actually be due to primary unidentified agents.

In this series, 10 (76.9%) patients had positive direct Coombs' test. The occurrence of Coombs' negative AHA is not unusual as this might be due to low or undetectable level of antibody or complement on the red cell membrane, using the conventional method [10]. An uncommon clinical presentation in patients with warm AHA is the occurrence of haemoglobinuria found in 6 of our cases. This further justified why the patients were screened for PNH. However, tests for cold agglutinin could also have excluded the possibility of mixed AHA known to be associated with severe haemolysis and haemoglobinuria [11]. Autoimmune haemolytic anaemia could also be related to drugs such as diclofenac (a non-steroidal anti-inflammatory drug) [12]. Although none of our patients gave a positive drug history, the ease with which drugs could be purchased over the counter in this environment makes such history unreliable.

Autoimmune diseases are said to be relatively more common in women than they are in males [13]. This study, however revealed almost equal sex prevalence, similar to the findings of Esan in Ibadan [2] and Sokol *et al.* [7]. Oestrogen has been incriminated to be responsible for the sex bias by a yet unknown mechanism [14].

Table 4: Management and outcome

SN	BTxR Units	Chemotherapy Pred.	CXT	DTBR weeks	PFU weeks	Outcome A/D
1	4	+	-	1	52	LFU
2	2	+	-	1	104	LFU
3	5	+	-	2	596	A
4	4	+	+	-	3	D
5	5	+	-	4	14	LFU
6	6	+	+	-	-	D
7	4	+	+	4	4	LFU
8	9	+	+	5	604	A
9	18	+	-	2	104	LFU
10	2	+	-	4	16	LFU
11	3	+	-	4	312	LFU
12	3	+	-	2	16	LFU
13	3	+	+	-	3	D

PFU - period of follow-up
A/D - alive/dead
BTxR - blood transfusion requirements
Pred. - Prednisolone
CXT. - therapy for the primary malignancy
DTBR. - Duration of therapy before remission
LFU - Lost to follow-up

All our patients presented with moderate-severe anaemia, which was life threatening in some instances, and required blood transfusion. Getting sero-compatible blood is a problem in AHA. However the least incompatible donor red cell is usually chosen [11], and patients are normally closely monitored during transfusion. Blood transfusion in AHA is not favoured by some [15]. Such clinicians fear the possibility of intensification of haemolysis from the immune antibodies, which can destroy both the autologous and allogenic red blood cells, and further alloimmunization as a result of the foreign antigens on the transfused red blood cells. The study of Salama *et al* [15] has allayed this fear. They found the incidence of alloimmunization as well as adverse haemolytic reaction to be less common in AHA patients than in the multitransfused patients.

Prednisolone was the main chemotherapectic agent used in all the cases (except those with primary malignancies who also received some other drugs for the primary malignancy). Clinical improvement was recorded in 10 (76.9%) patients treated, with remission of anaemia within 1-5 weeks of initiating therapy. Three deaths were recorded in patients with secondary AHA, due mainly to the primary disorders: two cases of stage IVB Hodgkin's disease and one of osteogenic sarcoma. The others were followed up for between < 1 and 604 weeks before the majority (81.8%) was lost to follow-up. Prognosis, especially in idiopathic AHA, could be said to be good. Association of AHA with thrombocytopaenia is referred to as Evan's syndrome [9]. This syndrome was found in 4(30.8%) patients, and has illustrated the close relationship of the two disorders in terms of pathogenesis.

This study agrees with the view that autoimmune disorders are not so common in indigenous African population as previously documented in Nigeria [9] and other parts of Africa [3]. The study also demonstrates the usefulness of prednisolone as first-line drug. Blood transfusion is indicated only in life-threatening anaemia.

Acknowledgements
We thank all our colleagues who took part in managing some of the patients with us.

References

1. Albert JL and Inman RD. Molecular mimicry and autoimmunity. N. Engl. J. Med. 1999; 341: 2068-2074.
2. Esan GJ. Autoimmune haemolytic anaemia in Nigerians. East Afr. Med. J. 1974; 51(10): 701-709.
3. Tsega E, Choremi H, Bottazzo GF and Doniach D. Prevalence of autoimmune diseases and autoantibodies in Ethiopia. Trop Geogr Med 1980; Sep; 32: 231-236.
4. Salawu L, Fatusi OA, Kemi-Rotimi F, Adeodu OO and Durosinmi MA. Familial Burkitt's lymphoma in Nigerians. Ann. Trop. Paediatr. 1997; 17:375-379.
5. Dacie JV and Lewis SM. Practical Haematology. 8th ed. Churchill Livingstone. Edinburgh. 1995; pp 445-464.
6. Luzzatto L and Hillmen P. In: Dacie JV, Lewis SM (ed). Practical Haematology. 8th ed. Churchill Livingstone. 1995; pp 287-295.
7. Sokol RJ, Hewitt S and Stamps BK. Autoimmune haemolysis: an 18- year study of 865 cases referred to a regional transfusion centre. B. Med. J. 1981; 282: 2032-2027.
8. Zupanska B, Lawkowicz W, Gorska B *et al*. Autoimmune haemolytic anaemia in children. Br. J. Haematol. 1976; 34: 511-520.
9. Packman CH and Leddy JP. Acquired haemolytic anaemia due to warm-acting autoantibodies. In: Beutler E., Lichtman MA, Coller BS, Kipps TJ (eds.) Williams Haematology 5th ed. Philadelphia. McGraw Hill Inc. New York. 1995; pp. 677-685.
10. Santhosh-Kumar CR and Kolhouse JF. Haemolytic anaemias. In: Wood ME, Bunn Jr. PA (eds.) Haematology/Oncology Secrets. Hanley & Belfus Inc. Philadelphia 1994; pp. 38-43.
11. Packman CH and Leddy JP. Cryopathic haemolytic syndromes. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ (eds). Williams Haematology. 5th ed. Philadelphia. Mc Graw Hill Inc. New York. 1995; pp. 685-691.
12. Salama A, Kroll H, Wittmam G and Mueller-Eckhardt C, Diclofenac-induced immune haemolytic anaemia: simultaneous occurrence of red blood cell autoantibodies and drug-dependent antibodies. Br. J. Haematol. 1996; 95: 640-644.
13. Jones WR. Autoimmune disease and pregnancy Australian and New Zealand Journal of Obs. & Gynaecology 1994; 34: 251-258.
14. Schwartz RS. Autoimmunity and Autoimmune Disease. In Paul WE (ed.) Fundamental Immunology. 3rd ed. Lippincott-Raven. Philadelphia and New York 1993; pp. 1033-1097.
15. Salama A, Berghofer H and Mueller-Echhardt C. Red blood cell transfusion in warm-type autoimmune haemolytic anaemia. Lancet. 1992; 340: 1515-1517.