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Immune Hemolytic Anemia

Amar Taksande*, Sneh Kumar, Varsha Sharma and Sachin Damke

Department of Paediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra State, India

ABSTRACT

The diagnosis of autoimmune haemolytic anaemia (AIHA) is a challenge for both the immune-haematology laboratory and the clinician as the laboratory investigation can be troublesome and often requires extensive time-consuming serological testing, especially when a blood transfusion is needed. Frequently, there is a need to start therapy rapidly. Autoantibodies directed to epitopes on red blood cell (RBC) consisting in sugar and/or protein structures are crucial in the pathogenesis of AIHA. The *isotype* is important for the clinical significance of an autoantibody. Frequently, patients are icteric and suffer from clinical signs of anaemia, such as pallor, fatigue, shortness of breath and palpitations, on examination hepatosplenomegaly can be present. If there is no vital indication for a transfusion it is prudent to wait for the results of the immune-haematological tests and the ensuing transfusion advice based on this. Focus of treatment should be stoppage of hemolysis or at least be attenuated via an inhibition of autoantibody production and/or inhibition of premature RBC destruction. Successful treatment of secondary AIHA is only possible when the underlying disease is treated.

***Corresponding author**

Amar Taksande, Department of Paediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra State, India. E-mail: amar.taksande@gmail.com

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Introduction

Autoimmune hemolytic anemia is a rare autoimmune disease in which autoantibodies directed toward red blood cell antigens lead to their accelerated destruction. AIHA can affect both children (mainly before the age of 5 years) and adults, and its annual incidence is estimated to be between 1-3 per 100,000 individuals [1-4]. It is characterized by an abnormal production of antibodies that bind to antigens on the erythrocyte surface. These antibodies then lead to the destruction of RBC, thus shortening their life span. Hemolytic anemia in newborn is characterised by abnormal production of antibodies in mother against the antigen on erythrocyte surface of baby (as newborn has weak immune response to make its own auto- antibodies) as compared to paediatric and adult immune system which is capable to generate its own auto-antibodies against the RBC's surface antigen [5, 6]. There are 60 different antigens are capable of eliciting antibody response but significant disease is associated with D antigen, ABO Factors, C and E antigen etc. Autoimmune hemolytic anemia is a term used for paediatric and adult population whereas for newborn immune hemolytic anemia is considered as better terminology [7]. The classification of the autoimmune hemolytic anemia is shown in table1 [8].

Table 1: Classification of AIHA

Autoimmune hemolytic anemia is classified as –
I. Warm reactive AIHA: Optimal reactivity of autoantibodies at 37 °C A. Primary or idiopathic B. Secondary • Associated with various lymphoproliferative disorders (e.g., non-Hodgkin's lymphoma, chronic lymphocytic leukemia) • Associated with rheumatic disorders (e.g., systemic lupus erythematosis (SLE) • Associated with non-lymphoid malignancies (e.g., ovarian cancer) • Associated with chronic inflammatory disorders (e.g., ulcerative colitis) • Drug induced autoimmune hemolytic anemia
II. Cold reactive AIHA: Optimal reactivity of autoantibodies below 37 °C A. Cold agglutinin syndrome i. Primary or idiopathic ii. Secondary • Post-infectious (e.g., mycoplasma or infectious mononucleosis) • Associated with B cell lymphoproliferative disorder B. Paroxysmal cold hemogloburina (Donath–Landsteiner syndrome)
III. Mixed type AIHA: Characterized by the presence of both warm and cold type autoantibodies A. Primary or idiopathic B. Secondary • Often associated with rheumatic disorders
IV. Drug induced AIHA: Associated with an estimated 150 drugs A. Drug dependent AIHA • Hapten or drug absorption • Immune (ternary) complex B. Drug independent AIHA

Clinical Presentation

Clinical presentation of immune hemolytic anemia is different in newborn and paediatric age group (Table 2) [9]. It is usually presented in one of two ways -

- **Acute transient** Generally seen in 70-80% cases, involving 2-12year of age group for 3-6 months. This variety is characterised by a persistent response to glucocorticoid medication, a low mortality rate, and complete recovery.
- **Prolonged chronic** More commonly seen in infants and children >12 year. The effect to glucocorticoid is imprecise and variable.

➢ Warm AIHA - It's a serious, life-threatening state characterized by pallor, jaundice, dark urine, and splenomegaly.

➢ Cold AIHA - This condition can be idiopathic, but it's more common when infections like M. pneumoniae (atypical pneumonia) as compared to lymphoproliferative disorders.

➢ Paroxysmal Cold Hemoglobinuria due to Donath Landsteiner Cold Hemolysin- An abrupt bout of hemolysis with a reduction in haemoglobin and hemoglobinuria is the most typical clinical finding. The haemoglobin reduction is typically severe enough to necessitate a transfusion (and this condition has been linked to sudden mortality).

Table 2: Clinical features of IHA

Paediatric age group	Newborn
• Pallor	• Hyperbillirubinemia
• Fatigue	• Hydrops Fetalis
• Fever	• Heart failure
• Confusion	• Shock
• Jaundice	
• Increase heart rate	
• Enlarged liver/spleen	
• Change in urine colour	

Warm Autoimmune Hemolytic Anemia [11-13]

- In the warm antibody type, the autoantibodies attach to and destroy RBC at temperatures equal to or in excess of normal body temperature, antibodies are activated at warm temperature of 37 degrees celsius, primarily leading to extravascular hemolysis.
- Usually associated with the development of IgG type of antibody (also IgA &IgM), IgG binds to RBC surface antigens, this drives monocytes & macrophages to grab and pick off portions of RBC membrane, RBCs become spherocytes, and destruction of RBC occur in spleen leading to extravascular hemolysis.

Cold Autoimmune Hemolytic Anemia

- In the cold antibody type, the autoantibodies become most active and attack red blood cells only at temperatures well below normal body temperature. In cold temperature, IgM binds to polysaccharide region of glycoproteins on RBC surface; these triggers complement system to lyse RBC.
- **Causes include**

o Infections (especially mycoplasmal pneumonia and infectious mononucleosis)

o Lymphoproliferative disorders (antibodies are usually directed against the I antigen)

o Idiopathic (usually associated with a clonal B-cell population) [5]

Cold Agglutinin Syndrome [6,7]

Cold hemagglutinin illness is most commonly caused by Mycoplasma pneumoniae infection, but it can also be caused by infectious mononucleosis, CMV, mumps, and other infections in rare cases. Cold hemagglutinin sickness, also known as IgM-induced hemolysis, is caused by antibodies that target the I/i system (red cell surface antigens). Anti-I is identified in infectious mononucleosis, while anti-I cold agglutinins are found in M. pneumoniae-associated hemolysis. The adhesion of Mycoplasma pneumoniae to the red cell membrane appears to be mediated by sialic acid-containing receptors linked to the I antigen's terminal galactose residues.

These auto antibodies are present to a lesser or greater degree in the serum of normal, healthy individuals. They do not react at body temperature, are reactive optimally at lower temperatures, and are often too weak to even be detected in serologic procedures. It is only significant in patients with the cold agglutinin syndrome.

The mechanism of cold agglutinin is as follows: when exposed to the cold, the cold auto antibody is activated, which causes agglutination of RBCs and fixes complement as the RBCs flow through the capillaries of the skin. This results in auto agglutination and signs of acrocynosis. Complement fixation may result in intravascular hemolysis. The hemoglobin and hematocrit results do not match. The RBCs count will be decreased due to double erythrocyte being counted as a single cell, thus resulting in a falsely high Mean corpuscular volume. Hematocrit will also be lowered, as the volume of doublets are slightly less than 2 cells. The Mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH) values will be increased due to decreased hematocrit and RBC count. The most common and easiest treatment for agglutinin syndrome is to avoid the cold, keep warm, or move to a warmer climate. In more severe cases, plasma exchange and corticosteroids for patients who's RBCs have been highly sensitive with C3. Alkylating drug chlorambucil has some favourable results as well. If blood transfusion is required, blood should be transfused warm.

Paroxysmal Cold Hemoglobinuria (PCH)

PCH is a rare type of cold antibodyhemolytic anemia. Destruction of RBC results from exposure to cold (28-31 degrees Celsius).
Occurs more in children, antibody involved is IgG type.
RBC's may be destroyed even when cold exposure is limited to a small area of the body, such as when the person drinks cold water or wash hand in cold water.
During certain infections, microbes trigger formation of antibody that reacts with the P antigen of RBC surface.
After the infection, these polyclonal anti-P autoantibody binds to P-Ag (antigen) of RBC in cold temperature, when temperature increased, complement system lyses these RBCs leading to intravascular hemolysis, which further cause anemia and hemoglobinuria [10,11].

Drug Induced Aiha [8,12]

Antibodies directed against the drug or one of its metabolites.
All may involve IgG antibody& C3 for hemolysis.The site of hemolysis is extravascular.

Investigations

Following investigations are required for diagnosing autoimmune hemolytic anemia

- CBC (haemoglobin, MCH, MCHC, hematocrit)
- Absolute reticulocyte count
- Coomb's Test (direct, Indirect)

- Hemosiderin in the urine
- Protein electrophoresis

All above mentioned investigations are required for diagnosing autoimmune hemolytic anemia in pediatric age group as well as in newborn except the indirect coomb's test is useful only in newborn as this test is done in mother to detect antibodies against fetal red blood cell antigen which get transferred through placenta from mother's blood in utero.

• Direct coomb's test (Direct antiglobulin test)

This test is used to determine whether the RBC-binding Autoantibody (IgG) or compliment (C3) is bound to Ag on RBC Membranes. Coomb's reagent is added to washed RBC's from the patient. If IgG or C3 is bound to RBC membranes, agglutination occurs and it is considered as a positive result (Diagram1).

• Indirect coomb's test (Indirect antiglobulin test)

The indirect antiglobulin (indirect Coomb's) test is a complementary test that consists of mixing the patient's plasma with normal RBCs to determine whether autoantibodies are free in the plasma (diagram1). Normal RBCs are added to patient's plasma, then Coomb's reagent is added, agglutination occurs if autoantibodies are present in patient's plasma, which is consider as positive test [12-14].

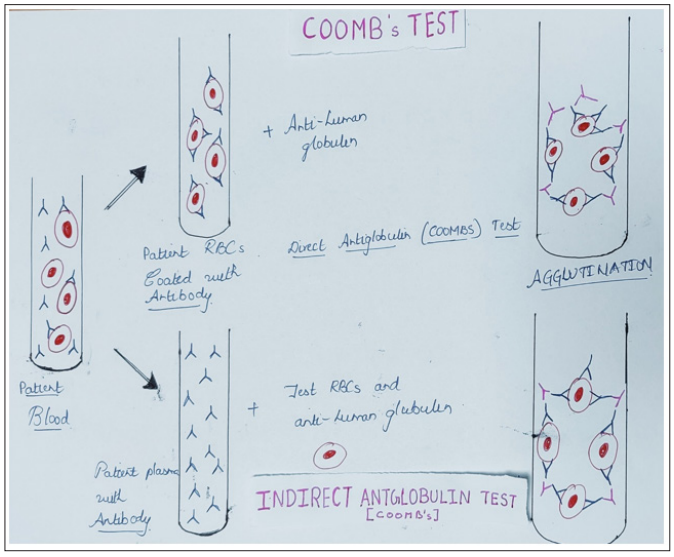

Figure 1: Direct and Indirect Coomb's test

Treatment

Warm Autoimmune Hemolytic Anemia

This could be a life-threatening situation, hence daily monitoring of hemoglobin level, reticulocyte count, splenic size, hemoglobinuria and haptoglobin level will be helpful in management. Monitoring of urine output, hydration status, cardiac status is required. Transfusion should be avoided whenever necessary because there will be no genuinely suitable blood available, and transfused cells' survival in this scenario is very restricted, and they may not be able to appreciably raise haemoglobin levels. Nonetheless, utilising the "least incompatible" blood may be essential in properly selected scenarios so that cardiopulmonary compromise is avoided.

About half of patients respond to corticosteroid medication within 4-7 days, however a small percentage of patients continue to have severe hemolysis during the first week after starting treatment. Tapering of steroid treatment should be considered when DCT becomes negative and the patient's haemoglobin concentration and reticulocyte count remain satisfactory. Alternative treatments should be sought for these patients, as well as people who appear to be dependent on steroids.

Rituximab is generally used in extensive cases not responding early to treatment or in patients exhibiting steroid dependence. In individuals with severe IgG-induced immune hemolytic anaemia, plasmapheresis has been shown to reduce the pace of hemolysis. If antibody manufacturing continues, the effect is short-lived, and success is limited. Immunomodulating agents like Mycophenolate mofetil, Cyclosporine, Danazol have shown positive results.

Drugs like Azathioprine, 6-mercaptopurine, Cyclophosphamide can be used to provide steroid sparing effect [10,14]. Intravenous Gammaglobulin should be given in individuals who have extensive hemolysis and require transfusion but have poor transfusion responses [11,12]. Splenectomy is recommended if the hemolytic process is progressing rapidly despite the administration of high-dose corticosteroids, rituximab, and transfusions, and the patient is unable to maintain a safe haemoglobin level, or if persistent hemolysis occurs. Although it should be avoided in young infants because of the high risk of sepsis and mortality

Cold Autoimmune Hemolytic Anemia

Primary cause should be controlled. Patients with severe hemolysis who are symptomatic may require transfusions. The patient's room should be warmed up. Hemolysis and peripheral agglutination can be reduced by keeping a patient warm. Because IgM is predominantly intravascular, plasmapheresis is particularly effective in the treatment of IgM illness. Plasmapheresis is recommended for patients with severe hemolysis.

Paroxysmal Cold Hemoglubinuria (PCH)

The mainstay of treatment is keeping a patient warm, and warming blood in a blood warmer prior to transfusion is critical [10-15]. Despite the fact that the condition is caused by an IgG antibody, patients with chronic severe hemolysis may benefit from plasmapheresis. Steroids should only be used in patients who are unresponsive to other treatments. Rituximab could be beneficial. As in newborns day of living and severity of hyperbilirubinemia are 2 important factors for bilirubin induced encephalopathy.

For example – if a 5-day old neonate came with serum bilirubin levels of 30mg/dl (DCT – Positive) with clinical features suggestive of encephalopathy like shrill cry, exaggerated reflexes, hypertonia/hypotonia, convulsions then 1st line of treatment will be exchange transfusion (If signs of encephalopathy is absent then iv immunoglobulin are 1st line of treatment considering the risk of blood transfusion related infections).

On the other hand if a 3 week old neonate came with serum bilirubin levels of 30mg/dl then we consider iv immunoglobin as 1st line of management because at day of life of 3 weeks blood brain barrier is developed so risk of encephalopathy is less and considering the blood transfusion related infections iv immunoglobulin is 1st line of management here.

Neonatal occurrence of AIHA is very rare. As AIHA is so rare, few data on clinical management and treatment strategies are available. The use of steroids is widely accepted, although long term treatment during infancy is associated with appreciable side effects, such as neurological and somatic growth retardation, hypertension, and hypertrophic cardiomyopathy. Table 3 shows the summary for treatment of AIHA.

Table 3: Summary for Treatment of AIHA

Treatment	AIHA in paediatric	IHA in newborn
1st line	Steroids	Immunoglobulin
2nd line	Immunoglobulin	Exchange transfusion
Other's	Rituximab, danazol, cyclosphosphamide, azathioprine &cyclosporine -treat the underlying etiology if any (infections) if above mentioned treatment is ineffective, splenectomy is also considered	steroids

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