Autoimmune Hemolytic Anemia (AIHA)
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What is AIHA?

• Increased destruction of erythrocytes due to the presence of anti-erythrocyte autoantibodies (AEA)
  • Decreased life span

• Multiple types
  • Primary, Secondary, Warm, Cold, Mixed, and Drug induced
Symptoms

- Onset typically slow
- Referable to anemia
- In secondary AIHA, symptoms of primary illness may overshadow
- Jaundice
- Splenomegaly ~20%

Erythrophagocytosis

[Image of erythrophagocytosis process]

Figure 1 Hematological Diseases

Epidemiology

- Annual incidence is approximately 1-3 cases per 100,000 people
- Primarily found in adults – More severe
  - Children with primary immunodeficiency
- Major is idiopathic
- Secondary-Malignant lymphoproliferative diseases, drugs, and viral infections
- No known predisposition

AIHA Subtypes

- Classification based on optimal RBC-autoantibody reactivity temperatures
- Warm and Cold AIHA more predominant
  - Warm is IgG (Opsinization) autoantibodies that bind optimally at 37°C
  - Cold is IgM (Complement) that strongly agglutinates at 4°C
    - Glucocorticoids
- Pathogenesis, diagnosis, and treatment vary greatly between subtypes
Warm AIHA (wAIHA)

- 1 in 80,000
- Predominant type found in children
- Secondary wAIHA – mononucleosis, HIV, and chronic lymphocytic lymphoma
- Optimal temperature of 37°C
- Usually associated with IgG (Also IgA and IgM)
  - The etiology underlying the pathogenesis of such autoantibodies is still unclear

wAIHA Continued

- Binding of self AB (Polyclonal) to Rh proteins, causing Fcγ receptors to mediate removal of RBCs within the spleen
- Imbalances in IL-10 and IL-12 believed to play a role
- Molecular mimicry
  - Exogenous antigens mimic an autoantigen (Influenza Virus)
  - Autoantibodies induced nonspecifically and transiently during microbial infections
wAIHA Mechanism

Cold AIHA (cAIHA)

- Caused by cold agglutinin syndrome (CAS) or paroxysmal cold hemoglobinuria (PCH)
- Less prevalent than wAIHA
- Mainly affects middle-aged or elderly
- Complement-dependent manner
  - I/i - Blood type that contains specific carbohydrates C3 proteins
  - Most are IgM (Formation of MAC)
  - Optimal temperature of 4°C
  - Presence of cold stress increases AEA activity, facilitating RBC lysis
  - Occurs often in extremities
Drug induced (diAIHA) and Mixed (mAIHA)

- Both rare
- diAIHA – associated with ~150 drugs
  - Hapten-type
  - Drug-autoantibody immune complexes
    - Methyldopa
- mAIHA – presence of warm and cold
  - IgM and IgG
Diagnosis

• Recognition of hemolysis and anemia
  • Jaundice and abnormally dark urine

• Direct antiglobulin test (DAT) or Coombs test
  • Anti-human globulins are used to assess the presence of antibody coated RBCs via agglutination
    • Polyclonal and monoclonal

• Possibly flow cytometry
  • Increased sensitivity for RBC-bound Ig detection

Direct Coombs test / Direct antiglobulin test

Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient’s washed RBCs are incubated with antihuman antibodies (Coombs reagent).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

Treatments

- Based on type of antibody involved (IgG, IgM, or IgA) and whether primary or secondary

- Fc receptor-competition – Intravenous infusion of IgG
  - The mechanism of the IVIG effect in AIHA appears to be related to the saturation of Fc phagocyte receptors in reticuloendothelial system that is amplified in AIHA patients

Treatments Continued

- Immunotherapy – the treatment of disease by inducing, enhancing, or suppressing an immune response
  - Classified as suppression immunotherapy if the immunotherapy reduces or suppresses the immune response
  - Corticosteroids or Rituximab
    - Rituximab is a humanized monoclonal antibody directed against CD20 on pre-B cells and mature B lymphocytes

- Severe anemia/ Other drugs will not work
  - High Dose immunosuppressive drugs and stem cell transplantation
Future Treatments

- More efficacious and less toxic
  - Soluble receptors, monoclonal antibodies, and molecular mimetics
- Possibly gene therapy
  - Multigenetic control
    - \textit{Aia-1} allele (chromosome 4)
    - Suppressive genes \textit{Aem-1, Aem-2, Aem-3}
    - Down-regulate production of AEA

Study Questions

1. Describe Autoimmune Hemolytic Anemia and the mechanism for the warm subtype.

2. Which of the following correctly describes the mechanism of Cold AIHA?
   a. The binding of warm IgG AEA to erythrocytes does not itself damage the erythrocytes
   b. Surface bound IgG is usually recognized by Fcy receptors of cells of the monocyte-macrophage phagocytic system, preferentially in the spleen and liver, resulting in uptake and destruction of IgG-opsonized erythrocytes
   c. IgM autoantibodies bind to \textit{l/i} carbohydrate on RBCs and form multivalent complex. Upon returning to the central part of the body the IgM complex detaches, leaving C3b, an opsonizing complement molecule. C3b then allows trapping and phagocytosis of RBC by kupffer cells.
Study Questions

3. Which is not a treatment or potential treatment for AIHA?
   a. The treatment of the disease using the drug Rituximab, which contains humanized monoclonal antibody directed against CD20 on pre-B cells and mature B lymphocytes and results in apoptosis of CD20 positive cells.
   b. The treatment of the disease using the drug Imiquimod, which activates the innate immune system through TLR-7 and can lead to the activation of B-cells through cell migration to the lymph nodes.
   c. Removal of the spleen to eliminate a large portion of potential autoerythrocyte antibody producing B-cells
   d. Gene therapy that utilizes suppressive genes to downregulate the production of anti-erythrocyte auto-antibodies

4. Which type of AIHA is the most common?
   a. Cold
   b. Mixed
   c. Warm
   d. Drug Induced
Study Questions

5. Which of the following statements about AIHA is false?
   a. Mixed AIHA involves the formation of hapten molecules that activate an immune response.
   b. The onset of symptoms of AIHA is typically slow, but can include dizziness, jaundice, and rapid heart beat.
   c. There is no race or gender component, no age pre-selection, and no identified genetic background for AIHA.
   d. The most common test for AIHA is the direct antiglobulin test (DAT), which utilizes anti-human globulins to detect the presence of antibody coated RBCs via agglutination.

Answers

1. Autoimmune Hemolytic Anemia is the increased destruction of erythrocytes due to the presence of anti-erythrocyte autoantibodies (AEA).
   1. Binding of self AB (Polyclonal) to Rh proteins, causing Fcγ receptors to mediate removal of RBCs within the spleen
   2. Imbalances in IL-10 and IL-12 believed to play a role

2. C
3. B
4. C
5. A
References


