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Original Research Article

Autoimmune hemolytic anemia in children during 2004–2014 in the Department of Pediatrics, Hematology and Oncology, Warsaw Medical University

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ABSTRACT

Introduction: Autoimmune hemolytic anemia (AIHA) is a rare disorder in which the immune system produces pathologic antibodies directed against its own red blood cells (autoantibodies). AIHA is most commonly diagnosed by a positive result of the direct antiglobulin test (DAT, Coombs test). Depending on the temperature at which autoantibodies react with red blood cells *in vitro* AIHA is classified as warm-type AIHA with incomplete IgG autoantibodies and cold-type AIHA with cold IgM agglutinins (CAS – cold agglutinin syndrome) or with biphasic hemolysins (PCH – paroxysmal cold hemoglobinuria). In mixed-type AIHA there are simultaneously warm autoantibodies and cold agglutinins.

Aim: The aim of this study was to find the number and types of AIHA diagnosed and treated in the Department of Pediatrics, Hematology and Oncology of Warsaw Medical University during the years 2004–2014.

Material and methods: The authors analyzed 54 children in which AIHA was diagnosed. The age of the child at diagnosis, the result of direct antiglobulin test and the type of autoantibodies in serum were taken into account.

Results and discussion: The most common type of AIHA in a group covered by the survey was cold-type AIHA, including paroxysmal cold hemoglobinuria (37%) and cold agglutinin syndrome (16%).

Conclusions: As far as the results are concerned, avoidance of cold is essential before the serological diagnosis is reached.

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1. Introduction

Autoimmune hemolytic anemia (AIHA) is an acquired hemolytic anemia in which the immune system produces pathologic antibodies against its own red blood cells shortening their survival time, either present in the plasma or completely bound to red cells.

It is a rare disease. The incidence is approximately 1–3 cases per 100 000 of population per year.[1–3] The diagnosis is based on typical clinical symptoms and the analysis of serological and biochemical results. The clinical picture of the disease is varied – from an acute, postinfectious, self-limiting type to chronic, lasting constantly for years or periodic hemolysis, with sudden relapses. During the relapse, severe hemolysis may be life threatening. During the chronic phase the immunosuppressive treatment is not always unreservedly effective; however, side effects are still commonplace.

The diagnosis of the disease is based on clinical features and the results of laboratory tests indicating hemolysis as a cause of anemia. In patients with AIHA, apart from anemia, there is jaundice. The jaundice is caused by an excessive increase of unconjugated bilirubin concentration as a result of red blood cells destruction. The patient's dark-colored urine is related to hemolobinuria or the presence of bile pigments in urine. The results of laboratory tests state decreased concentration of hemoglobin, reduced amount of red blood cells and increased percent of young red blood cells – reticulocytes.[4] The concentration of haptoglobin is reduced, whereas lactate dehydrogenase and aspartate aminotrasferase concentrations are increased.

The direct antiglobulin test (DAT, Coombs test) is the screening test that allows the immune nature of the hemolysis to be identified. However, the negative result of DAT does not exclude AIHA.[5] In some cases, the autoantibodies against red cells cannot be displayed in standard serological tests and AIHA is diagnosed whether from typical clinical features.[6] On the other hand, a positive DAT plus anemia does not necessarily mean that the patient has autoimmune hemolytic anemia.[7]

Precise and insightful analysis of the activity of autoantibodies and their thermal properties allows to distinguish AIHA into groups.[6,8–10] Depending on the temperature at which the autoantibodies react *in vitro* with red blood cells, AIHA is classified as warm-type AIHA with incomplete IgG autoantibodies and cold-type AIHA with cold agglutinins (cold agglutinin disease) or with biphasic hemolysins (paroxysmal cold hemoglobinuria).[2,3,9] Some cases, however, escape this classification, such as the mixed-type AIHA in which the hemolysis is sustained by both warm and cold autoantibodies.[11] Serologic features of autoantibodies in AIHA are presented in Table 1.

The method of treatment depends on the type of AIHA and the severity of clinical symptoms and these are presented in Table 2.

1.1. *Warm-type AIHA*

Warm-type AIHA is the most common type of AIHA, observed in about 75% of cases.[8] The disease can be distinguished into primary (idiopathic) and secondary forms, the last predominately in association with lymphoproliferative disorders, infections, immunodeficiency states and autoimmune disorders such as systemic lupus erythematosus. In this type of AIHA, Coombs test is usually positive and reveals autoantibodies IgG associated with C3d component of complement system.[12] In the majority of patients incomplete IgG autoantibodies which bind to erythrocytes most avidly at 37°C[3,12–16] are detected in plasma. In this type of AIHA the hemolysis is extravascular – red blood cells are destroyed by phagocytosis in the reticuloendothelial system, primarily in spleen, and later in liver.[6,17] Warm-antibody AIHA is characterized by great variability in terms of onset, grade of severity and clinical course. The onset of idiopathic forms is often insidious, although in some patients it may be sudden, with rapidly worsening anemia and jaundice. Moreover, we can observe enlargement of spleen or liver and spleen. Life-threatening hemolytic episodes are more common in AIHA cases secondary to infections. Massive, usually short-lasting hemoglobinuria may also occur in acute cases, albeit rarely. Some patients may be not significantly anemic and indeed may be symptomless. Purpura is not commonly found, except in Evans' syndrome, in which AIHA is associated

Table 1 – Serologic features of autoantibodies in AIHA.

Classification	Warm type	Cold type	Paroxysmal cold hemogobinuria	Mixed type
Antibodies (Ig)	IgG	IgG	IgM	IgG+IgM/IgA
DAT	IgG, IgG+C3d	C3d	C3d, IgM	IgG, IgM, IgA, C3d

Table 2 – Characteristics of main clinical features of AIHA.

	Clinical manifestations	Treatment
Warm-type AIHA	Mild to severe anemia, sometimes acute hemolysis	Good response to corticosteroids, immunosuppressive therapy, blood transfusions
Cold agglutinins disease	Moderate, dependent of exposure to cold	Avoidance of cold, immunosuppressive therapy, intravenous IgG, blood transfusions only when necessary
Paroxysmal cold hemoglobinuria	Acute hemolytic anemia, often with significant reduction of hemoglobin concentration, hemoglobinuria	Supportive care (avoidance of cold, antibiotics if signs of infection), blood transfusions if needed, a short course of corticosteroids if hemolysis is severe