EPIDEMIOLOGY AND RISK FACTORS OF WARM AND COLD AUTOIMMUNE HEMOLYTIC ANEMIA

Abstract. Even though clinical features in autoimmune haemolytic anaemia vary according to the type of AIHA, anaemic syndrome stays common for most of the cases. A positive Coombs test or direct anti-globulin test developed in 1945 by Coombs, Mourant and Race, is the most deciding factor in AIHA diagnosis. Since the immunologic mechanisms causing erythrocyte destruction vary between AIHAs, treatment is also different. Empirical approach with glucocorticoids is the main treatment of AIHA overall, but less effective in CAD. However, the current medical literature is still with gaps concerning the management, presentation and diagnosis of the different types of AIHA altogether.

Keywords: Autoimmune haemolytic anaemia, Warm antibody autoimmune haemolytic anaemia, cold agglutinin disease.

INTRODUCTION

Autoantibodies directed against erythrocytes cause autoimmune haemolytic anaemia (AIHA), which can be caused by complement activation or not. Depending on the antibody's thermal amplitude, isotype, and ability to fix complement, as well as bone marrow compensation, the clinical picture can vary from mild/compensated to life-threatening anaemia. Steroids, immunosuppressant’s, and splenectomy have been the mainstay of treatment for a
few years. Several target therapies are increasingly being used in clinical practice or are being developed in clinical trials in recent years. As a result, a large number of refractory/relapsed cases have accumulated, posing a clinical challenge. Moreover, the need to harness therapy has become a necessity due to the availability of several drugs acting on the different pathophysiologic mechanisms of the disease. During the various stages of the disease, it is especially important to determine the best medication option, sequence, and/or combination. Relapsed/refractory cases, in particular, can mimic pre-myelodysplastic or bone marrow failure syndromes, indicating that immunosuppressant’s should be used with caution, and vice versa, recommending bone marrow immunomodulation/stimulating agents. Despite advances in diagnostic methods, diagnosis of DAT-negative AIHAs and assessment of disease-related risk factors for relapse and mortality remain unmet needs. In comparison to malignant hematologic disorders, it has traditionally been known to be a trouble-free disease that is easy to treat and has a low clinical effect. Due to many immunological mechanisms involved beyond antibodies, complement, and antibody-dependent cell-mediated cytotoxicity, AIHA has been described as a highly heterogeneous disease. The importance of bone marrow compensation, as well as bone marrow characteristics that can expose dyserythropoietic marrow, fibrosis, and clonal lymphoproliferation, has increased in recent years. Finally, AIHAs have been linked to a variety of conditions (lymphoproliferative, autoimmune and infectious disorders, immunodeficiency’s, solid tumours, transplants, and drugs) in which multiple immunologic pathways are involved in an unpredictable way. The recent availability of next-generation sequencing has enhanced the diagnosis of many related conditions while also the proportion of “secondary” vs. “primary” AIHAs. All of these recent discoveries about the disease's pathogenesis and therapeutic options have undeniably altered the AIHA landscape [1].

The Coombs test, also known as the direct antiglobulin test (DAT), is the gold standard for diagnosing AIHA. It allows the disease to be classified based on the isotype and thermal characteristics of the autoantibody. Warm AIHA (wAIHA), the
The most powerful indicator of relapse has been described as the magnitude of anemia at the time of onset. Complement involvement and the autoantibody's thermal characteristics were also significant, with warm IgG + C, mixed, CAD, and atypical types requiring second or additional therapy lines more frequently. Furthermore, the involvement of immune thrombocytopenia (Evans syndrome) is linked to a higher risk of relapse and treatment refractoriness. Furthermore, the presence of reticular fibrosis, dyserythropoietic marrow, and hyper cellularity in the bone marrow has been linked to shorter relapse-free survival and a lower response rate to immunosuppressive therapies. Hb 6 g/dL at onset, Evans' syndrome, multiple lines of treatment, acute renal failure, and infections have all been linked to an increased risk of death by 5-8 fold.

**EPIDEMIOLOGY AND RISK FACTORS**

AIHA is a relatively rare disease with a currently estimated incidence of 1.77 cases per 100,000 populations per year and 0.2 cases/1,000,000 in individuals under 20 years of age [2]. Old nations which has its age structure changing, having more number of older population like in the U.S., has an estimated incidence of about 2 per 100,000 per year [3]. Incidence is directly proportional with increasing age of population which is given in the figure 1. Thus, AIHA is more in people above 40 years of age. It is also seen more commonly in early childhood due to a relatively weak immune system. According to a French study, incidence of AIHA in children under age 18 was estimated to be 0.81/100,000 per year [4].

In children, there is some evidence of an occurrence of the disease within some families in excess, but no hereditary genetic background has yet been found. The course of AIHA only lasts for a short time in early childhood are mostly associated with viral infections. Other children frequently develop AIHA due to an underlying autoimmune disease. Primary AIHA and Evans syndrome (ITP associated with AIHA) have more prevalence in women and children.
Chronic and relapsing cases in adults are more frequent especially in secondary AIHAs. Adults with AIHA, properly managed happen to have good prognosis. According to recent studies on prognosis of AIHA, 91% of adults live up to one year, 75% for five years, and 73% for 10 years. Infections, concurrently occurring, AIHA with thrombocytopenia (Evans syndrome), acute renal failure, and major thrombotic events (pulmonary embolism, stroke, cardiac infarction) are bad prognosis factors for AIHA patients. Recent reports stated a mortality rate of 4% in overall AIHA cases [5]. Rare cases requiring ICU admissions, mostly due to warm AIHA has also been reported in 5% of overall AIHA cases and despite all therapeutic efforts, recent estimates suggest that mortality is about 30–57% in such rare cases. Patients undergone splenectomy has shown increased risk of future thrombotic events in 15–20% of AIHA cases overall.

The most common serological type, warm AIHA is reported in 65–70% of all AIHA cases. Warm AIHA consist of about 80–90% of adult cases and 50% of paediatric cases [6,7,8]. The median age of onset for WAHA is 52 years, but it can happen at any age with a slight female predominance [9]. As per a study by Lawrence and team, annual warm AIHA incidence is estimated to be around one per 75,000-
80,000 population, occurring in people of all ages. A recent report stated that the prevalence of warm AIHA in seven countries (Germany, France, Italy, Spain, and the United Kingdom) was 82,045 cases in 2017 [10]. The total diagnosed warm autoimmune haemolytic anaemia prevalence was observed to be around 28,924 in the United States, with 9,641 males and 19,283 females. In terms of type-specific warm AIHA prevalence in the US, primary warm autoimmune haemolytic anaemia prevalence was estimated to be around 10,847 cases, whereas secondary warm AIHA prevalence was estimated around 18,078 cases. A low share in the number of patients having spontaneous remissions or treatment-induced long-term remissions along with a low death rate has led to a relatively high prevalence of 17 per 100,000 in Denmark.

The next common AIHA after warm AIHA is CAD. Cold AIHA is reported in 20-25% of AIHA cases. The incidence of chronic cold agglutinin disease (CAD) is estimated to be 1 per million per year, with a female prevalence. The annual incidence of AIHA is estimated at 1/35,000-1/80,000 in North America and Western Europe. A higher incidence of CAD in Northern climates is suggested. It is more common in elderly and it has a chronic course in contrast with warm AIHA. According to recent study, the incidence and prevalence of cold AIHA in cold climates showed a fourfold increase than incidence and prevalence of cold AIHA in warm climates but with less evidence to confirm the data [11].

Secondary AIHAs account for 40-50% of AIHA cases and the rest is primary AIHA. Secondary AIHA associated with hematologic malignancy accounts about 50% of cases, most frequently reported with chronic lymphocytic leukaemia (5%-10%) in which the female to male ratio is low, non-Hodgkin lymphoma (2%-3%), and Hodgkin lymphoma (0.2%). Secondary AIHAs associated with infections comprise of 35% of all reported cases. AIHAs associated with infection caused by mycoplasma or EBV were reported in 3% of all secondary AIHAs. Other autoimmune conditions were reported in 15% of secondary AIHAs, out of which 5-10% were SLE patients in which female to male ratio is very high [12,13]. 2%-4% of cases of allogeneic hematopoietic stem-cell transplantation also reported secondary AIHA [14].
Genetic background, immunodeficiency, autoimmune disease, infections, medication - especially novel anti-cancer drugs, neoplasia - especially CLL (5-10% cases) or NHL (13–19%) and transplants are common risk factors suggested based on different studies [2,15,16]. One of the main single risk factor for developing AIHA is ageing. A recent study on the association of COVID-19 with autoimmune diseases, showed evidence of onset of AIHA post COVID-19 infection, but still it is rare. It was found that, the RBC structural membrane protein ankyrin (ANK-1) shared an epitope that is 100% identical to the SARS-CoV-2 spike surface glycoprotein. Many studies stated that elderly patients with co-morbidities were having a less efficient adaptive immune system and more prone to develop autoimmunity after getting infected by COVID. Immunosenescence, the gradual deterioration of immune system as we age, and epigenetic abnormalities on haematopoietic stem cells are believed to be the reason behind age related increased risk for AIHA and at the same time increased risk of elderly patients with COVID infection to develop AIHA [17-19].

Reference:
1. F. B. Barcellini W, "The Changing Landscape of Autoimmune Hemolytic Anemia," Front Immunol, vol. 11, p. 946, 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7325906/
2. S. S. Michalak, A. O. Gawlik, J. R. Matysek, E. W. Rokicka, E. Nowakowska and L. Gil, "Autoimmune hemolytic anemia: current knowledge and perspectives," Immunity and ageing, vol. 17, no. 38, pp. 1-16, 2020. https://immunityageing.biomedcentral.com/articles/10.1186/s12979-020-00208-7
3. J. L. Jameson, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo and J. Loscalzo, Harrison's principles of internal medicine 20th edition, New York: Mc Graw Hill Education, 2018. https://accessmedicine.mhmedical.com/book.aspx?bookID=2129
4. J. M. B. C. F. H. J. J. C. G. e. a. Aladjidi N, "Reliable assessment of the incidence of childhood autoimmune hemolytic anemia," Pediatr Blood Cancer, vol. 64, no. 12, pp. 1-19, 2017. https://pubmed.ncbi.nlm.nih.gov/28748541/
5. W. Barcellini, A. Zaninoni, J. A. Giannotta and B. Fattizzo, "New Insights in Autoimmune Hemolytic Anemia: From Pathogenesis to Therapy," J Clin Med., vol. 9, no. 12, p. 3859, December 2020. https://pubmed.ncbi.nlm.nih.gov/28748541/
6. C. H. Packman, "The Clinical Pictures of Autoimmune Hemolytic Anemia," *Transfus Med Hemother*, vol. 42, no. 5, p. 317–324, 2015. https://www.karger.com/Article/Fulltext/440656

7. S. Ladogana, "Diagnosis and management of newly diagnosed childhood autoimmune haemolytic anaemia. Recommendations from the Red Cell Study Group of the Paediatric Haemato-Oncology Italian Association," *Blood Transfus*, vol. 15, no. 3, pp. 259-267, 2017. https://pubmed.ncbi.nlm.nih.gov/28151390/

8. K. TA, "Warm antibody autoimmune hemolytic anemia," *Hematology Am Soc Hematol Educ Program*, vol. 2016, no. 1, pp. 690-697, 2016. https://pubmed.ncbi.nlm.nih.gov/27913548/

9. R. A. Brodsky, "Warm Autoimmune Hemolytic Anemia," *N Engl J Med*, vol. 381, no. 7, p. 647–54, 2019. https://www.nejm.org/doi/full/10.1056/NEJMc1900554

10. DELVEINSIGHT BUSINESS RESEARCH LLP, "Warm Autoimmune Hemolytic Anemia Epidemiology forecast segmentation, treatment approaches, and WAIHA market forecast." DELVEINSIGHT, 2020. https://www.delveinsight.com/blog/warm-autoimmune-hemolytic-anemia-epidemiology-forecast/

11. S. Berentsen, W. Barcellini, S. D'Sa, U. Randen, T. H. A. Tvedt, B. Fattizzo, E. Haukås, M. Kell, R. Brudevold, A. E. A. Dahm, J. Dalgaard, H. Frøen, R. F. Hallstensen, P. H. Jæger, H. Hjorth-Hansen, A. Malecka, M. Oksman, J. Rolke, M. Sekhar, J. H. Sorbø, E. Tjønnfjord, G. Tsykunova and G. E. Tjønnfjord, "Cold agglutinin disease revisited: a multinational, observational study of 232 patients," *Blood*, vol. 136, no. 4, p. 480–488, 2020. https://www.uptodate.com/contents/cold-agglutinin-disease/abstract/1,39

12. R. E. J. B. L. E. S. H. H. J. I. W. J. A. M. E. S. a. S. A. A. Hoffman, "Hematology: Basic Principles and Practice," Elsevier, Philadelphia, 2018. https://www.elsevier.com/books/hematology/9780323357623

13. B. W. B. C. G. M. H. A. H. Q. J. B. K. D. M. M. M. R. A. Z. S. B. S. Jäger U, "Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting," *Blood Rev*, vol. 41, p. 100648, 2020. https://pubmed.ncbi.nlm.nih.gov/31839434/

14. Dynamed, "Ipswich (MA)," EBSCO Information Services, 4 December 2018. [Online]. Available: https://www.dynamed.com/topics/dmp~AN~T900221 [Accessed 24 January 2021].

15. W. Barcellini, J. Giannotta and B. Fattizzo, "Autoimmune hemolytic anemia in adults: primary risk factors and diagnostic procedures," *Expert Review of Hematology*, vol. 13, no. 6, pp. 585-597, 2020. https://www.tandfonline.com/doi/abs/10.1080/17474086.2020.1754791

16. B. Fattizzo, J. A. Giannotta, F. Serpenti and W. Barcellini, "Difficult Cases of Autoimmune Hemolytic Anemia: A Challenge for the Internal Medicine Specialist," *J Clin Med*, vol. 9, no. 12, p. 3858, 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7760866/
17. L. S. M. G. A. C. d. M. E. M. A. C. F. Angileri F, "Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19?," *Br J Haematol*, vol. 190, no. 2, pp. e92-e93, 2020. https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.16883

18. L. Omarjee, F. Perrot, O. Meilhaç, G. Mahe, G. Bousquet and A. Janin, "Immunometabolism at the cornerstone of inflammaging, immunosenescence, and autoimmunity in COVID-19," *AGING*, vol. 12, no. 24, p. 26263–26278, 2020. https://www.aging-us.com/article/202422/text

19. K. D. K. J. H. F. Y. Wada T, "Overexpression of the shortest isoform of histone demethylase LSD1 primes hematopoietic stem cells for malignant transformation," *Blood*, vol. 125, no. 24, p. 3731–46, 2015. https://ashpublications.org/blood/article/125/24/3731/34008/Overexpression-of-the-shortest-isoform-of-histone