Current treatment options for severe autoimmune hemolytic anemia

Cite this article as: Yeşilbaş O. Current treatment options for severe autoimmune hemolytic anemia. Turk Pediatri Ars 2018; 53: 129-31.

Dear Editor,

I have read the article of Özdemir et al. (1) published in the final issue of your journal with interest. I primarily congragulate the authors for their efforts. On account of this case presentation, I would like to draw attention to current treatment of severe autoimmune hemolytic anemia (AIHA) in the accompaniment of the literature published in recent years.

In warm antibody AIHA, IgG type antibodies bind to erythrocyte surfaces at 37 ˚C and cause mostly splenic hemolysis and extravascular hemolysis. The first line treatment for this subtype in current guidelines is steroids. Currently, rituximab is recommended instead of splenectomy which was formerly the second line treatment (2, 3). Use of high dose steroid and intravenous immunoglobulin (IVIG) is recommended in patients with warm antibody AIHA in whom the course is severe and rapid hemolysis develops. Therapeutic plasma exchange (TPE) is recommended in unresponsive patients (2, 4).

In the case presented by the authors, IgM type autoantibodies lead to agglutination and hemolysis of erythrocytes by adhering to erythrocyte surface with complement (C3b) opsonization at low temperature (3-4 ˚C) in cold antibody AIHA (cold agglutinin disease) which the authors were focused on and which frequently occurs secondary to infections (1, 2, 4, 5). Unlike warm antibody type, hemolysis mostly occurs intravascularly and in the liver. In current treatment of cold agglutinin disease (CAD), primary and preventive tretment consists of enabling the patient to avoid cold environments, warming the patient and rapidly treating the underlying disease and infections. In medical treatment, steroid is not recommended as the first line treatment and splenectomy is not recommended as the second line treatment unlike warm antibody AIHA. The reason for this is the fact that a high rate of steroid unresponsiveness is observed and hemolysis occurs intravascularly and in the liver rather than in the spleen. In current treatment guidelines, rituximab is recommended alone or in association with non-steroid immunosupressive drugs (including fludarabine/cyclophosphamide/azathioprine) as the first line treatment in CAD (2, 4, 5). In severe CAD, TPE is recommended as preventive treatment until these treatments are initiated or if surgery during which hypothermia is predicted to develop, is needed. By way of therapeutic plasma exchange, autoantibodies causing intravascular hemolysis and complements activated by immune complexes can be eliminated and hemolysis can be rapidly stopped for short term (4, 5). In the guideline of the American Society for Apheresis published in 2016, it is recommended that albumin equivalent to 1-1.5 plasma volume should be used as replacement fluid during TPE (4). Again, the same guideline warns that blood may get cold inside the set or filter where plasma is separated while performing TPE in CAD and thus hemolysis may increase. For prevention of this, the room temperature should be increased or the set should be warmed (4). Based on all these aspects, I think that IVIG or TPE could be used alone as the first line treatment instead of high dose steroid in the pediatric patient presented in the article (1). In addition, the first session could be performed with albumin equivalent to 1.5 plasma volume in this pediatric patient who had a severe course, after the decision for this invasive treatment which is generally applied in pediatic intensive care unit and requires en experienced team, was made. Although transfusion was not needed after treatment, I think that at least three sessions of TPE would be appropriate, because signs of hemolysis continued (increased lactate dehydrogenase and decreased haptoglubulin). The authors reported that they discontinued steroid treatment in one week, direct coombs test was negative and the patient had no

problem at the follow-up visit performed one month later (1). Considering the shipment date of the article, it is understood that at least two years have passed after the patient's discharge. Reporting of the developments which have occured during this period and if the patient currently receives medication will be beneficial for us, clinicians.

Osman Yeşilbaş

Unit of Pediatric Intensive Care, Health Sciences University, Van Training and Research Hospital, Van, Turkey

References

1. Özdemir ZC, Bör Ö, Dinleyici EÇ, Kıral E. Plasmapheresis in a child with cold antibody autoimmune hemolytic anemia: Case report. Turk Pediatri Ars 2017; 52: 169-72.
2. Barcellini W. Current treatment strategies in autoimmune hemolytic disorders. Expert Rev Hematol 2015; 8: 681-91.
3. Ducassou S, Leverger G, Fernandes H, et al. Benefits of rituximab as a second-line treatment for autoimmune haemolytic anaemia in children: a prospective French cohort study. Br J Haematol 2017; 177: 751-8.
4. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the writing committee of the American Society for apheresis: the seventh special ıssue. J Clin Apher 2016; 31: 149-62.
5. Berentsen S. Cold agglutinin disease. Hematology Am Soc Hematol Educ Program 2016: 226-31.

Address for Correspondence: Osman Yeşilbaş
E-mail: drosmanyesilbas@gmail.com
Received: 08.11.2017
Accepted: 09.02.2018

DOI: 10.5152/TurkPediatriArs.2018.6499

Re: Current treatment options for severe autoimmune hemolytic anemia

Dear Editor,

We thank the valuable author for their opinions and recommendations related to our article. We would primarily like to report that our patient is in remission and recurrence has not occurred. The patient is still being followed up by us and the hemoglobin, reticulocyte, and bilirubin levels have been found to be normal, the direct Coombs test became negative and has not become positive again.

The author mentioned the treatment methods recommended for cold agglutinin disease, which is a type of autoimmune hemolytic anemia (AIHA). This disease, observed mostly in adults, is a chronic lymphoproliferative disease that develops idiopathically or secondary to other diseases including malignancy (1). At this point, we would like to emphasize that our patient had AIHA secondary to infection rather than cold agglutinin disease. As we mentioned in the first sentence of the part Discussion, AIHAs that develop secondary to infection mostly occur 2-3 weeks after onset of infection and recover spontaneously in 2-3 weeks (2). Negative Coombs test and lack of development of hemolysis during the follow-up supports that our patient did not have cold agglutinin disease.

Autoimmune hemolytic anemia may have a fatal course and the type of treatment should be specified according the severity and speed of development of anemia. There is no standard therapeutic approach because randomized controlled studies in children are lacking. Antibody specification tests are time-consuming procedures in children presenting with a clinical picture of autoimmune hemolytic anemia. Therefore, it is important to initiate treatment urgently until antibody specification tests are completed. Treatments administered in the acute phase include transfusion of erythrocyte suspension, corticosteroids and intravenous immunoglobulin (3). Corticosteroid treatment is mostly recommended in warm antibody AIHA (3). In a large-scale study conducted with children with autoimmune hemolytic anemia, it was reported that complete remission was obtained in 58% of the children with steroid treatment alone (4). In another recent study recently, it was reported that a good response to steroid was obtained in children regardless of the type of AIHA (5). The role of intravenous immunoglobulin in treatment is controversial. It has been recommended to consider the use of intravenous immunoglobulin G (IVIG) in patients who are resistant to steroid treatment (3). However, one of the main determinative factors in treatment is the type of antibody. In cold antibody AIHA, avoidance from cold and therapeutic plasma exchange are recommended as the first-line treatment and rituximab is recommended as the second-line treatment (3). On the other hand, cold agglutinin disease/cold antibody AIHA are included in the category II disease group; therapeutic plasma exchange is recommended alone or in combination with other treatments as the second-line treatment in this group of diseases according to the guidelines of the American Society for Apheresis (ASFA) Apheresis Applications Committee, published in 2016 (6).

In conclusion, AIHA may have a fatal prognosis in children. Prompt treatment is necessary. It would be appropriate to make treatment decision according to the clinical course and treatment response.

Zeynep Canan Özdemir, Özcan Bör, Ener Çağrı Dinleyici, Eylem Kıral

[1]**Department of Pediatrics, Division of Pediatric Hematology and Oncology, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey**

[2]**Department of Pediatrics, Pediatric Intensive Care and Infectious Diseases Unit, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey**

References

1. Bernstein S. How I manage cold agglutinin disease. Br J Haematol 2011;153: 309-17. [CrossRef]
2. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol 2002; 69: 258-71. [CrossRef]
3. Chou ST, Schreiber AD. Autoimmune hemolytic anemia. In: Orkin SH, Fisher DE, Look T, (eds). Nathan and Oski's hematology and oncology of infancy and childhood. 8th ed. Philadelphia: WB Saunders, 2015.p. 411-30.
4. Aladjidi N, Leverger G, Leblanc T, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265. Haematologica 2011; 96: 655-63. [CrossRef]
5. Sankaran J, Rodriguez V, Jacob EK, Kreuter JD, Go RS. Autoimmune Hemolytic Anemia in Children: Mayo Clinic Experience. J Pediatr Hematol Oncol 2016; 38: 120-4. [CrossRef]
6. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the writing committee of the American Society for apheresis: the seventh special issue. J Clin Apher 2016; 31: 149-62. [CrossRef]

Address for Correspondence: Zeynep Canan Özdemir
E-mail: efecanan@yahoo.com
Received: 18.02.2016
Accepted: 06.09.2016

DOI: 10.5152/TurkPediatriArs.2018.2121