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AUTOIMMUNE HEMOLYTIC ANEMIA WITH WARM ANTIBODIES IN CHILDREN*

Retrospective Analysis of 51 Cases

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SUMMARY: Gürgey A, Yenicesu İ, Kanra T, Özsoylu Ş, Altay Ç, Hiçsönmez G, Yetgin S, Tuncer M, Gümrük F, Çetin M. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Autoimmune hemolytic anemia with warm antibodies in children: retrospective analysis of 51 cases. Turk J Pediatr 1999; 41: 467-471.

In this paper, research based on 51 children with a positive antiglobulin test is presented. Eighteen of the children had acute anemia and 33 had chronic anemia. Two clinical patterns were distinguished: an acute transient type and a prolonged chronic type. Corticosteroid therapy was effective in all acute cases but its results were variable in the chronic cases. The acute form was more frequent in young children, while chronic autoimmune hemolytic anemia (AIHA) occurred mainly among children at puberty. In the chronic form of the disease, it was sometimes necessary to add immunosuppressive drugs and in two cases to perform a splenectomy. *Key words: autoimmune hemolytic anemia, Coombs' test, warm antibody.*

Autoimmune hemolytic anemia (AIHA) is a rare disorder in childhood and adolescence, and it has been shown by some of the clinical and laboratory findings to be quite different from adult AIHA[1]. Antibodies of the IgG are usually responsible for autoimmune hemolytic anemia in children. We would like to report here on the retrospective evaluation of 51 children with AIHA.

Material and Methods

This study reviews 51 children with AIHA whose ages ranged between two months and 16 years (median 6.2±5.35 years) and who were seen at Hacettepe University, Ihsan Doğramacı Children's Hospital between 1975 and 1996.

The patients were selected if they fulfilled the following criteria:

1. Clinical and laboratory onset of hemolysis prior to 16 years of age.
2. A positive direct and indirect antiglobulin test.
3. An adequate clinical and hematological follow-up.

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They were divided into two groups based on the duration of the disease, as a) acute transient cases if complete resolution of the disease was obtained within six months and b) chronic cases, of a duration longer than six months.

Routine hematological tests were carried out by standard procedures, immunohematological studies were conducted using previously described methods, and a battery of serologic tests were done for infectious diseases[2]. Immunologic investigations were done in 23 cases.

Results

Acute transient cases. Acute cases were diagnosed in 18 children (13 males and 5 females), whose ages at onset of the disease ranged from two months to 16 years (median 6.26±5.58) (Table I).

Table I: Age and Sex Distribution of 51 Patients with AIHA

	Acute Form n*=18	Chronic Form n=33	Total n=51
Male/Female	13/5	14/19	27/24
Age (years)			
<2	5 (9.8%)	5 (9.8%)	10 (19.6%)
3-5	5 (9.8%)	7 (13.7%)	12 (23.5%)
6-10	6 (11.7%)	6 (11.7%)	12 (23.5%)
11-16	2 (3.9%)	15 (29.4%)	17 (33.3%)
Total	18 (35.2%)	33 (64.7%)	51 (100%)

*n: number.
AIHA: autoimmune hemolytic anemia.

In half of the 18 patients, onset of AIHA was during the first five years of life. In five (27.7%) of the patients, hemolysis was observed after an upper respiratory tract infection (URTI). Parvovirus, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were identified in only three patients (Table II); a causative organism could not be identified in the others. Some of the clinical and hematological data of the patients at the time of diagnosis are shown in Table III. Constant physical findings were pallor, tachycardia and jaundice. Moderate splenomegaly and hepatomegaly were noted in 11 patients. Hemoglobin levels ranged from 2.8 g/dl to 9.2 g/dl. Sixteen patients received steroid therapy (2 mg/kg prednisolone), and two patients who did not respond to a standard dose of steroid therapy were treated with intravenous immunoglobulin (1 of them was also given a high dose of methylprednisolone - 30 mg/kg/day for 7 days). One patient in each group had Evans' syndrome. Exchange transfusion was performed in two patients

(1 of them was also treated with steroid), and both died of profound hemolysis shortly after the procedure. One patient with mild hemolysis received no therapy and recovered spontaneously in a short period of time.

Table II: Associated Disorders in Patients with AIHA

	Acute	Chronic
URTI	5	2
CMV	–	1
EBV	–	2
SLE	–	3
JRA	–	3
Immune deficiency	–	2
Autoimmune disease	–	3
Chronic hepatitis	–	1

AIHA: autoimmune hemolytic anemia,
URTI: upper respiratory tract infection, CMV: cytomegalovirus, EBV: Epstein-Barr virus, SLE: systemic lupus erythematosus, JRA: juvenile rheumatoid arthritis.

Follow-up studies disclosed total permanent recovery in 16 patients. Interestingly, Hodgkin's disease developed in one patient nine years after the diagnosis of AIHA.

Chronic cases. This group included 33 children (14 males and 19 females) whose ages at onset of the disease ranged from five months to 16 years (median 6.8±5.9). Fifteen patients were above 11 years of age. None of the patients had a family history of AIHA. The clinical and hematological data of the patients at the time of presentation are shown in Table III. In two patients hemolysis occurred during the course of URTI. In 12 patients associated disorders were observed during the follow-up period. Six patients developed collagen disorders (3 systemic lupus erythematosus [SLE], 3 juvenile rheumatoid arthritis [JRA] and immunodeficiency (1 common variable immunodeficiency, 1 selective immunoglobulin M deficiency). Autoimmune diseases were associated in another five patients, and chronic persistent hepatitis was observed in one patient (Table II). Steroid was prescribed for all patients, and four were also given a high dose of methylprednisolone (HDMP). At the time of subsequent attacks, 10 patients (2 had HDMP) remained sensitive to the steroid but the effect was transient. Splenectomy was performed in two patients who were resistant to prednisolone therapy. In both patients hemolysis was completely cured following splenectomy. Immunosuppressive agents, 6-mercaptopurine and azathioprine were administered to two patients in whom hemolysis could not be controlled by standard or HDMP. Remission was obtained within one month. Unfortunately, three patients with associated disorders died. They suffered cerebral involvement of SLE, intestinal perforation (in a patient with immune deficiency), and disseminated CMV infection (in a case with immune deficiency).

Table III: Initial Clinical and Hematological Data in Acute and Chronic Cases

	Number of Patients	
	Acute (n=18)	Chronic (n=33)
Pallor	12	20
Jaundice	4	4
Splenomegaly	7	4
Hepatomegaly	7	3
Hemoglobinuria	3	2
Anemia 8-11 g/dl	3	30
<8 g/dl	15	3
Reticulocytosis <5%	10	31
>5%	7	2
Reticulocytopenia (<1%)	1	–
Direct antiglobulin test (+)	15	21
Indirect antiglobulin test (+)	3	12
Thrombocytopenia (<100,000/μl)	1	1

Discussion

Autoimmune hemolytic anemia occurs less commonly in children and adolescents than in adults[1]. Among children the peak incidence is the first five years of life[3]. Among our subjects, 41 percent of all (both acute and chronic) cases were diagnosed before the age of five years. In the present study, 64.7 percent of cases followed the chronic course (Table I). This figure has been reported to be as high as 74 percent during childhood in some previous studies[3-4]. Among the chronic cases, the majority were older than 11 at the onset of the AIHA. In the same age group, only two patients (10%) followed the acute course. It seems that the disease follows a chronic course in patients older than 11 years of age. In seven patients, hemolysis followed after upper respiratory tract infections. This finding is similar to those of the other studies[5]. CMV infection was found in only two patients with immune deficiency syndrome; it was not found to be an important etiological factor in our study group. AIHA associated with underlying chronic disorders was seen in 12 patients with chronic AIHA in our series. Multiple autoimmune disorders were observed in three patients whose cases have been reported previously[6], and Hodgkin's disease, which is well known to be associated with AIHA, developed nine years after AIHA in one patient[7]. It has been reported that thrombocytopenia occurred in about 14-32 percent of patients with autoimmune hemolytic anemia[8]. In this study thrombocytopenia was documented in two of our patients; reticulocytopenia was also observed but in only one patient. Autoantibodies directed against erythroid progenitors or precursors are thought to have been responsible for the reticulocytopenia[9].

Response to steroid therapy was observed in 16 of 18 of our patients with the acute form, and 10 patients with the chronic form showed a temporary improvement. Exchange transfusion was unsuccessful in two patients because of profound hemolysis leading to cardiac failure. It has been reported that if antibody production is an ongoing process, the effect of exchange transfusion or plasmapheresis is transient; success is limited possibly because more than half of the IgG is present in the extravascular compartment[10]. Several reports indicated that intravenous immunoglobulin (IVIG) may be useful in selected patients[10]. In our series, two patients received IVIG and steroid therapy together. A complete cure of hemolysis was observed in both patients.

Removal of the major site of red cell destruction has been shown to be an effective therapeutic strategy in IgG-induced hemolytic anemia, with a success rate of approximately 50 to 70 percent[10]. Therefore, splenectomy was performed in two of our patients who were resistant to steroid therapy, and a complete remission was obtained in both. Several chemotherapeutic agents have been used in the treatment of childhood AIHA[10]. Our two patients received 6-mercaptopurine and azathioprine and complete remission was achieved.

In conclusion, our study showed that chronic AIHA occurred mainly in older children and females. Corticosteroid was effective in the acute form of the disease but none of the chronic cases recovered fully. However, splectomy and immunosuppressive agents produced a clinical cure in patients with the chronic disease. Although the number is too small to be conclusive, it seems that splenectomy, immunosuppressive agents and IVIG should be used in the treatment of chronic cases if they are resistant to corticosteroid therapy.

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