Study of Autoimmune hemolytic Anemia in Egyptian children

Thesis

Submitted for Partial Fulfillment of
M.Sc. Degree in Pediatrics

By

Maram Mohammed Abd El-hay Refaie

(M.B. & B.ch.Cairo University-2003)

Supervised By

Prof.Dr. Mona Hasan El-Tagy
Professor of Pediatrics
Cairo University

Ass.Prof.Dr.Heba Hassan Abou-Elew
Ass.Prof. of clinical pathology
Cairo university

Ass.Prof.DR. MONA KAMAL EL-GHAMRAWY

Ass.Prof. of Pediatrics
Cairo University

Department of Pediatrics
Faculty of Medicine
Cairo University

2010

بسْم الله الرَّحمَن الرَّحيم

"قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم"

صَدق الله العَظيم

سورة البقرة..الآيه ٣٢

Acknowledgment

*First, grace and foremost thanks are duo to **ALLAH,** most Gracious, most merciful, for blessing this work, as a part of **His** generous help throughout our lives.*

*I would like to express my sincere gratitude and respect to Professor Doctor **MONA HASAN EL-TAGY**, Professor of Pediatrics, Cairo University, for her continuous guidance and supervision, her kind encouragement and support throughout the entire period of the study.*

*It was an honor to have the support of Professor Doctor **SAMIA SALAH ,** Professor of Pediatrics, Cairo University, for her Kindness and help during working in the pediatric Rheumatology clinic.*

*It is my pleasure to express my unlimited appreciation and deepest thanks toAss.Professor Doctor **HEBA HASSAN ABOU-ELEW** , Ass.Professor of Clinical pathology, Cairo University, for her continuous supervision and great help.*

*I do appreciate the kind participation of Ass,Professor Doctor **MONA KAMAL EL GHAMRAWY**, Ass.Professor of Pediatrics, Cairo University, for the effort she exerted to help me and for her guidance and great support throughout the whole period of the study.*

I am indebted to every patient included in this study and also their parents for their corporation and their trust. I wish them all the best of health and happiness.

I am deeply grateful to my family, colleagues and friends.

Lastly, I would like to thank everyone who helped in completing this work.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AIHA	Autoimmune hemolytic anemia
ADCC	Antibody dependent cell mediated cytotoxicity
ALT	Alanine transferase
ANA	Antinuclear antibody
ANCA	Anti neutrophilic cytoplasmic antibody
AntiDNA	Anti deoxy ribonuclic acid
ASMA	Anti smooth muscle antibody
AST	Aspartate transferase
ALPS	autoimmune lymphoproliferative syndrome
BUN	Blood urea nitrogen
CAD	Cold agglutinin disease
CBC	Complete blood count
CLL	chronic lymphocytic leukemia
CMV	Cytomegalovirus
CT scanning	Computerised tomography
DAT	Direct antiglobulin test
DIIHA	Drug-induced immune hemolytic anemia
D-L	Donath-Landsteiner
EBV	Epstein-Barr virus
ESR	Erythrocyte sedimentation rate
HLA	Human leucocytic antigen
HIV	Human immunodeficiency virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IQR	Inter quartile range
IVIG	Intravenous immunoglobulin
Hb	Hemoglobin
LDH	Lactic acid dehydrogenase
MoAb	Monoclonal antibody
NRBC	Nucleated red blood cell
PCH	Paroxysmal cold hemoglobinuria
RBC	Red blood cell
SLE	Systemic Lupus Erythematosis
SPE	Serum protein electrophoresis
VZV	Varicella-zoster virus

Abstract

Autoimmune hemolytic anaemia is characterized by production of autoantibodies directed against erythrocyte membrane antigens.

The aim of the work is to study retrospective & prospective the clinical picture ,immunologic findings ,different lines of treatment ,and outcome of Autoimmune hemolytic anaemia patients treated in hematology clinic & other departments of Abo-elreesh hospital during one year interval.

Key Words: Autoimmune hemolytic anaemia – children – clinical picture- Investigation - treatment

Introduction

Autoimmune hemolytic anemia (AIHA) consists of a group of diseases which have, as their common factor, the presence of autoantibodies that bind to red blood cells and lead to its premature destruction by promoting their removal from the circulation by macrophages from the reticuloendothelial system ***(Klemperer, 1984).***

These occur after antibodies and/or complement components bind to red blood cell (RBC) surface antigens and thereby initiate RBC destruction via the mononuclear phagocytic system (extravascular hemolysis) or within the circulation (intravascular hemolysis) ***(Glader, 2006).***

The clinical presentation of AIHA depends on the subclass type and on the thermal range activity of the causative auto-antibody, so that two main pictures occur usually: warm auto-antibody and cold auto-antibody types, the latter being less frequent than the former ***(Rochant, 2001).***

Autoimmune hemolytic anemias are classified as primary or secondary. In primary AIHA, hemolytic anemia is the only clinical finding and no underlying systemic disease is observed that could explain the presence of autoantibodies ***(Mitra et al., 2000).***

Secondary AIHA occurs against the background of a systemic disease, and the hemolytic anemia is just one manifestation of that disease. It can affect patients with autoimmune diseases such as systemic lupus erythematosus, or other autoimmune inflammatory diseases, such as ulcerative colitis (***Mitra et al., 2000).***

It is also observed in patients with neoplasms such as Hodgkin's and non-Hodgkin's lymphomas, chronic lymphocytic leukemia, myelodysplastic syndromes, immunodeficiency, infection by *Mycoplasma, Epstein-Barr* virus, *Cytomegalovirus*, or drug usage ***(Palanduz et al., 2002).***

Diagnosis is based on a positive direct Coombs test in the presence of hemolysis. The direct Coombs test can, however, be negative in 2% to 4% of cases and has 8% false positives ***(Sackey, 1999)***.

No decisive advancement in therapy has arisen over the last decades. Some patients are still resistant to all therapeutic maneuvers and may die. Much labour is to be done in order to discover more rational methods of therapy to restore a state of normal tolerance towards erythrocyte auto-antigens. Suppressing the production of pathogenic auto-antibodies by immunomodulation may be the first step of this task ***(Rochant, 2001).***

Aim of Work

The aim of this work was to evaluate patients with autoimmune haemolytic anemia presenting to the pediatric haematology clinic of children hospital, Cairo University during a period of one year, regarding the demographic data, etiological background, clinical and laboratory presentation, different treatment modalities used, clinical course and outcome of the disease.

Autoimmune Hemolytic Anemia: General considerations

Definition:

Autoimmune hemolytic anemia (AIHA) is a type of hemolytic anemia where the body's immune system attacks its own red blood cells (RBCs)**,** leading to premature red cell destruction ***(Schick 2009, and Ware et al., 2009).***

AIHA is also known as immune hemolytic anemia, acquired hemolytic anemia, immune mediated anemia, and idiopathic autoimmune hemolytic anemia ***(Moore, 2006).***

Specific characteristics of the autoantibodies, especially the type of antibody; its optimal binding temperature; and whether complement is fixed influence the clinical picture. In all cases of AIHA, however, the autoantibody leads to a shortened red blood cell survival (i.e. hemolysis) and, when the rate of hemolysis exceeds the ability of the bone marrow to replace the destroyed red cells, anemia and its attendant signs and symptoms develop ***(Ware et al., 2009).***

Epidemiology:

From the beginning of the century, AIHA was the first model of an auto-antibody mediated disease ***(Rochant, 2001).*** The occurrence of AIHA in children and adolescents, however, is rare **(Oliveira et al., 2006).**

The exact incidence is unknown, but it is estimated that the rate is around 0.2 per 1,000,000 individuals under 20 years old **(Oliveira et al., 2006),** rendering it more common than acquired aplastic anemia but less

common than immune thrombocytopenic purpura (***Ware et al., 2009).*** This incidence rises with age, but most of the increase is a reflection of the secondary hemolytic anemias as opposed to idiopathic ***(Neff, 2003).***Peak incidence is among pre-school aged children ***(Sackey, 1999)***. Warm autoantibodies are responsible for most cases of AIHA ***(Petz, 2004).***

AIHA can affect children of any race or nationality and can present in infancy, especially after an infection, and throughout childhood ***(Sokol et al., 1984).*** Teenagers who present with AIHA are more likely to have an underlying systemic illness **(Oliveira et al., 2006)**.

Causes:

A number of extrinsic agents and disorders may lead to premature destruction of RBCs.The most important immune hemolytic disorder in pediatric practice is hemolytic disease of the newborn (erythroblastosis fetalis), caused by transplacental transfer of maternal antibody active against the RBCs of the fetus, that is, isoimmune hemolytic anemia ***(Segel, 2008)***.

Various other immune hemolytic anemias are autoimmune (Table 1) and may be idiopathic or related to various infections (Epstein-Barr virus, rarely HIV, cytomegalovirus, and mycoplasma), immunologic diseases (systemic lupus erythematosus SLE, rheumatoid arthritis), immunodeficiency diseases (agammaglobulinemia, autoimmune lymphoproliferative disorder, dysgammaglobulinemias), neoplasms (lymphoma, leukemia, and Hodgkin disease), or drugs (methyldopa, L-dopa). Other drugs (penicillins, cephalosporins) cause immune hemolysis that is not "autoimmune."***(Segel, 2008)***.

Classification of AIHA:

When AIHA occurs as the only disorder it is known as primary AIHA. When AIHA develops in patients who have another associated medical condition, is called secondary AIHA ***(Moore, 2006).***

Two basic subtypes of AIHA have been identified: 1) warm antibody hemolytic anemia and 2) cold antibody hemolytic anemia. Here, warm and cold refer to the temperature at which the autoimmune cell destruction occurs. Warm antibodies cause 80-90 percent of AIHA, and cold antibodies cause the remaining cases ***(Moore, 2006).***

A working classification of AIHA relates to the thermal properties of the offending antibodies: warm AIHA versus cold AIHA (Table 1). Cold AIHA can be further categorized into cold agglutinin disease and paroxysmal cold hemoglobinuria ***(Glader, 2006).***

According to the type of antibodies:

Autoimmune hemolytic anemia (AIHA) occurs when a patient produces pathologic antibodies that attach to and lead to the destruction of RBCs, causing anemia For AIHA to be present, both pathogenic antibodies and associated erythrocyte consumption must occur ***(Neff, 2003).***

AIHA may be classified into two major categories according to the optimal temperature of antibody activity: warm-reacting autoantibodies (usually IgG) optimal around 37 °C and cold-reacting autoantibodies, optimal at 4 degrees °C (usually IgM). This classification guides the selection of tests and treatment ***(Philippe, 2007).***Warm active antibodies have their greatest affinity at 37°C. Warm antibodies are typically of the IgG variety, may or may not fix complement, and primarily lead to RBC loss by splenic removal of the sensitized cells ***(Neff, 2003).***

Table (1): Classification of Immune Hemolytic Anemias:

Cold active antibodies

1. **Cold agglutinin disease**
   - **Primary or idiopathic**
   - **Secondary**
     - i. **Lymphoproliferative diseases**
     - ii. **Autoimmune disorders**
     - iii. **Infections**
       Mycoplasma pneumoniae
       Infectious mononucleosis
       Other viruses

2. **Paroxysmal cold hemoglobinuria**
   Syphilis
   Measles, mumps, other viruses

Mixed cold and warm active antibodies

Warm active antibodies

1. **Idiopathic autoimmune hemolytic anemia**
2. **Secondary autoimmune hemolytic anemia**
   - i. **Lymphoproliferative disorders**
   - ii. **Autoimmune disorders**
   - iii. **Other malignancies**
   - iv. **Viral infections**
   - v. **Immune deficiency states**

Drug-induced hemolytic anemia

1. **Drug adsorption type (penicillin)**
2. **Neoantigen type (quinidine/stibophen)**
3. **Autoimmune type (alpha-methyldopa)**

(Neff , 2003)

Conversely, cold active antibodies typically have little, if any, activity at body temperature but display increasing affinity for the RBC as the temperature approaches 0°C ***(Neff, 2003).***

Although notable exceptions occur, as a general rule, cold active antibodies are generally of the immunoglobulin (Ig) M type, fix complement, and may lead to immediate intravascular destruction of erythrocytes or their removal from the circulation by the liver ***(Neff, 2003).***