Introduction

Thalassemia intermedia encompasses a wide clinical spectrum of β-thalassemia phenotype. Some thalassemia intermedia patients are asymptomatic until adult life, whereas others are symptomatic from as young as 2 years of age.A number of clinical complications commonly associated with thalassemia intermedia are rarely seen in thalassemia major, including extramedullary hematopoiesis, leg ulcers, gallstones and thrombophilia. Prevention of these complications is ideal since they may be difficult to manage ***(Taher et al., 2006)***.

Currently, many patients with thalassemia intermedia receive only occasional or no blood transfusions, since they are able to maintain hemoglobin levels between 7-9 g/dl; the risk of iron over load, necessitating adequate chelation therapy, is also a contributing factor. At present, there are no clear guidelines for initiating and maintaining transfusions in thalassemia intermedia for

the prevention or treatment of complications ***(Cappellini et al., 2007)***.

Splenectomy might be needed sometimes because of hypersplenism and mechanical encumbrance ***(Aessopos et al., 2005b)***.

The cost of providing lifelong medical care to the patients with thalassemia according to the standards adopted in the developed countries is extremely high. The burden of thalassemia imposed in the health systems of the developing countries is unbearable ***(Kattamis, 2007)***.

The need for therapeutic interventions alternative to chronic blood transfusion and iron chelation therapy for these patients is urgent ***(Wetherall, 2005)***.

Reactivation of HbF is successful alternative. Hydroxyurea appears to be the most effective drug for this purpose ***(Kattamis, 2007)***.

Stem cell transplantation is an option limited to the severe forms. Gene therapy and other molecular approaches are

subjects of intense study ***(Borgna-Pignatti, 2007)***.

Aim of the Work

The aim of this study was to assess the phenotypic variability of Egyptian children with thalassaemia intermedia, their clinical characteristics as well as frequency of complications in comparison to age and sex matched thalassemia major patients. The study assessed also the clinical and hematological response to treatment of TI patients with fetal hemoglobin inducers (such as hydroxyurea and L-carnitine).

Thalassemia

Definition

The thalassemias are a diverse group of disorders characterized by a reduced synthesis of one or more of the globin chains that form the oxygen-carrying hemoglobin molecules found in red blood cells ***(Kanavakis and Traeger-Synodinos, 2007)***.

Thalassemias are inherited anemias caused by mutation at the globin gene loci on chromosomes 16 and 11, affecting the production of α- or β-globin protein respectively. The thalassemia syndromes are named according to the globin chain affected or the abnormal hemoglobin produced. Thus, β-globin gene mutations give rise to β-thalassemia and α- globin mutations cause α-thalassemia ***(Cunningham, 2008)***.

Historical background

Thalassemia was defined as a clinical entity in 1925 when Dr. Thomas B. Colley and his associate Pearl Lee, Pediatricians

at the Detroit Children's Hospital, presented a paper at the annual meeting of the American Pediatric society describing five young children with severe anemia, splenomegaly and peculiar bone abnormalities ***(Cooley and Lee, 1925)***.

Two years later, in 1927, Cooley published his classic paper in American Diseases of Childhood that described seven children with distinctive features that indicated they represented a new syndrome. Their common features included a peculiar facies resembling the Mongolian race, with a yellow skin color and thickening of facial bones and malar eminences. The thickening of the calvarial and long bones had a unique and distinctive roentgenographic appearance ***(Cooley et al., 1927)***. He also observed that his patients were Italian ethnicity, and he suggested the names erythroblastic or Mediterranean anemia for the disease that was subsequently given his name.

Following Cooley's epochal descriptions, other similar conditions were reported in North America and Europe. In 1932, Whipple and Bardfod in Rochester, New York, described pathological findings

in several children. Apparently wishing to avoid the eponym "Cooley's anemia," they coined the term "thalassemia" from the Greek word ***(thalss)***, meaning "the sea" (i.e., the Mediterranean). Thus, thalassemia means "the sea in the blood" ***(Whipple and Bradford, 1932).***

Whipple and Bradford 1936

"Thalassemia"

Θαλασσα

The sea in the blood

Figure (1): Why it was called thalassemia
(Quoted from Pearson, 1996).

Shortly after Cooley's report was published a series of related papers appeared in the Italian, Greek and American medical literature. Rietti, Greppi, and Micheli described individuals with a mild, familial, microcytic anemia with increased RBC osmotic resistance. Caminopetros in Greece recognized a similar blood condition and showed that it was recessively transmitted ***(Caminopetros, 1938).***

It was shortly thereafter that Gatto in Italy and Valentine and Neel in the

United States clearly pointed out the relationship of these mild microcytic anemias to the severe Cooley's anemia and suggested the clinical terms thalassemia "minor" and "major" for the heterozygous and homozygous conditions ***(Gatto, 1942)***.

Global epidemiology

Thalassemia is among the most common genetic disorders worldwide; 4.83 percent of the world's population carries globin variants, including 1.67 percent of the population who are heterozygous for α-thalassemia and β-thalassemia. Thus, the worldwide birth rate of people who are homozygous or compound heterozygous for symptomatic globin disorders is not less than 2.4 per 1000 births, of which 1.96 have sickle cell disease and 0.44 have thalassemias ***(Angastiniotis and Modell, 1998)***.

Similar to sickle cell disease and G6PD deficiency, the high prevalence of α- and β-thalassemia genotypes is believed to be a consequence of an evolutionary protection of heterozygotes against death from plasmodium falciparum malaria ***(Clegg***

and Weatherall, 1999). Before the twentieth century, thalassemia tracked with areas of malarial prevalence. β-thalassemia arose in the Mediterranean, Middle East, South and Southeast Asia and Southern China ***(Cunningham, 2008)***. α-Thalassemia originated in Africa, the Middle East, China, India and Southeast Asia. Immigration and emigration, however, had led to change in the demographics and patients who have thalassemia syndrome and heterozygote carriers resided in all parts of the world ***(Vichinsky et al., 2005)***.

Special concerns with respect to our Middle Eastern populations

1. Middle East definitions:

The Encyclopedia Britannica states, "The term Middle East had come to be applied to the lands around the southern and eastern shores of the Mediterranean Sea, extending from Morocco to the Arabian Peninsula and Iran and sometimes beyond." The Britannica definition was similar to that of the US State Department definition with the addition of Cyprus, Turkey and Sudan (Figure 2) ***(Steensma et al., 2001)***.

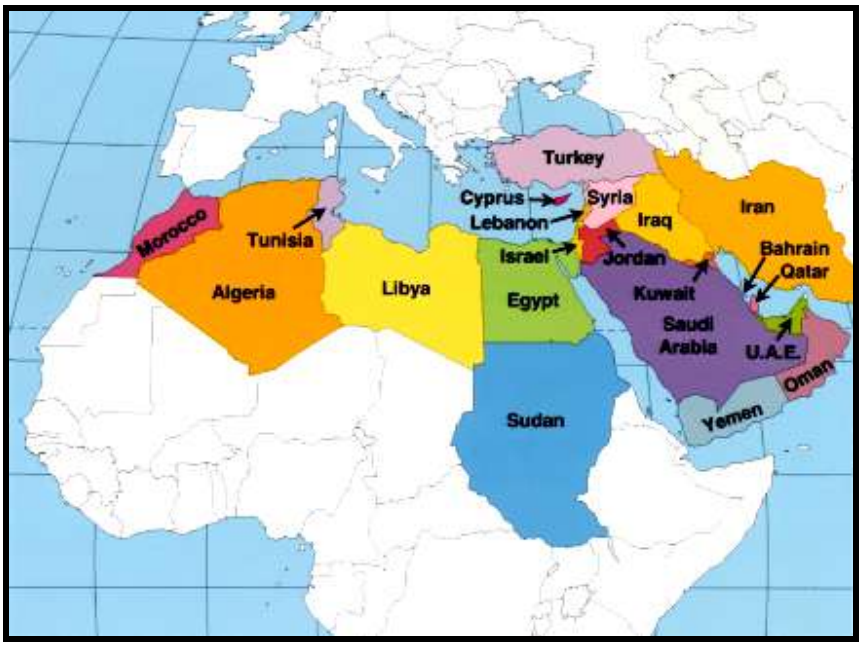

Figure (2): The Middle East, as defined by the US State Department ***(Steensma et al., 2001)***

The region had traditionally been divided into a western zone (the Maghrib, which encompasses North Africa till west of Egypt) and an eastern zone (the Mashriq, extending from Egypt to Iran). The World Health Organization's Eastern Mediterranean Region included most of the states in the Mashriq and some in the Maghrib ***(Steensma et al., 2001).***

2. Prevalence of hemoglobinopathies in the Eastern Mediterranean region

The World Health Organization estimated that approximately 5% of the population in the Eastern Mediterranean Region had a hemoglobin disorder. There was extensive local variation within the region, however (***Steensma et al., 2001)***. Table 1 shows some data on the prevalence of hemoglobinopathies in the Eastern Mediterranean Region.

Table (1): Percentage of the population in the World Health Organization's Eastern Mediterranean Region with an abnormal hemoglobin*

Proportion of population	Country
>10%	Cyprus (17%), Bahrain (13%)
6%-10%	Saudi Arabia, Morocco, Sudan, Iraq, Oman, Qatar, Syria, Yemen
4%-6%	Tunisia, United Arab Emirates, Pakistan, Libya, Iran, Kuwait, Lebanon
<4%	Jordan, Afghanistan, Egypt, Ethiopia

* These figures include thalassemias and hemoglobinopathies but not enzymopathies (such as G6PD deficiency, which affects tens of millions of people) or membrane disorders. Numbers rounded to the nearest whole percent ***(Data derived from Angastiniotis and Modell, 1998).***

In Egypt, β-thalssemia is the most common genetically determined, chronic hemolytic anemia. The actual number of patients surviving to date is not, however, available ***(El-Beshlawy et al., 2007).***

3. Annual affected conceptions with thalassemia syndromes worldwide and in Eastern-Mediterr-anean Region according to Bulletin of the World Health Organization (June 2008)

Worldwide, hemoglobin disorders were originally endemic in 60% of 229 countries, potentially affecting 75% of births, but are now sufficiently common in 71% of countries among 89% of births (either in the whole population or among minorities). Annually there were about 56000 affected conceptions with a major thalassemia including α and β thalassemia including at least 30000 who need regular transfusions to survive and 5500 who die perinatally due to α thalassemia major which require policy-makers to consider the most appropriate strategy for treatment and prevention. Table (2) represents the annual affected conceptions with thalassemia syndromes in Eastern-Mediterranean region ***(Modell and Darlison, 2008).***

Table (2): Annual affected conceptions with thalassemia syndromes in Eastern-Mediterranean region.

WHO and component regions	Annual affected conceptions	
	β-thalassemias	α-thalassemias
Eastern-Mediterranean region	9 715	1
Northern Africa (including Egypt)	1 829	0
Eastern Africa	19	0
Western Asia	1 815	1
South central Asia	6 053	0

(Quoted from Modell and Darlison, 2008)

4. The estimated reach of treatment for β thalassemia worldwide and in Eastern Mediterranean region

Worldwide, there were about 12% of children born with transfusion – dependent β-thalassemia are actually transfused and less than 40% of those transfused obtain adequate iron chelation therapy. About 100000 patients are currently living with regular transfusions and at least 3000 die annually in their teens or early 20s from uncontrolled iron overload. Table (3) shows the estimated reach of treatment for β-thalassemia in Eastern Mediterranean

region (including Egypt) as defined by WHO ***(Modell and Darlison, 2008).***

Table (3): Estimated reach of treatment for β-thalassemia in Eastern Mediterranean WHO's region

WHO region	Estimated annual births with β thalassemias		Transfusion			No. of known patients	Adequate iron chelation		Inadequate or no iron chelation	
	Total	Transfusion dependent	Annual no. starting transfusion	% of transfusion dependent patients transfused	Annual deaths because not transfused		% with chelation	No. with chelation	No. of patients	Annual deaths due to iron overload
Eastern Mediterranean	9914	9053	1610	17.8	7443	39700	27	10818	28882	1444

(Quoted from Modell and Darlison, 2008)