بسم الله الرحمن الرحيم

Shiraz University of Medical
Sciences School of Dental Medicine

Oral & Maxillofacial surgical management of Beta-Thalassemia patient

Thesis :

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Advisor

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DEDICATED TO

My self-sacrificing parents, the most valuable teachers of my life, whose excellent guidance and precious encouragement enabled me to find my path of life.

And dedicated to
my kind sister
&
my devoted brothers.

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INTRODUCTION

In the name of God whose benevolence led to accomplishment of this thesis.

First of all, I would take the opportunity of making due acknowledgement to all my dear professors. I must also thank my dear professor Dr Behzad Rahsepar who has made a great contribution to this work.

The aim of this thesis is to study the systemic and dental management of β-thalassemic patients and to seek for the types of surgery suitable for correcting the complications of these patients. Therefore , at first, an introduction to this disease and a brief history of it, together with the definition, classfication and prevalence of the disease have been given. As the disease. is caused by disorders in hemoglobin, a brief study of hemoglobin and its types seemed to be necessary.

Then I have discussed the pathophysiology related to the disease. The study of disorders and complications of these patients, after I have dealt with pathophysiology, would give a clear understanding of their problem.

On the other hand, diagnosis is of great importance and achieved through clinical features, labratory features, radiographic findings and

oral manifestations.

Oral manifestions in diagnosis is very important to the dentist and should be taken into consideration for two reasons:

1. To cure the patients with regard to their problems and points which should be taken in to account when dealing with these patients.
2. As these patients need blood transfusion, there is the probablity of contagious diseases such as **hepatitis**, AIDS,... .Due attention to thalassemic patients and taking preventive measures eliminates any risk for the dentist.

The study of management of these patients appears at the end of the thesis; this includes systemic and dental managemant, and also post-operative considerations.

Finally, it should be noted that few articles were available on thalassemia with regard to dentistry. Therefore I have tried to make use of as many sources and researches as possible, so that the thesis can be used by those who are interested in the subject.

HISTORY

A form of severe anemia ocurring early in life and associated with splenomegaly and bone changes was first described by Cooly and Lee in 1925. The condition was later named thalassemia.(1)

Thalassemia is made up of two parts, thal in greek means sea and emia means blood, because the first reports was occured in Mediterranean area.

After 1940 that the true genetic character of this disorder was fully appreciated. It be came clear that the disease described by Cooly and Lee is the homozygous state for a partially dominant autosomal gene for which the heterozygous state is associated with much milder hematologic changes.(1)

Today, more recently it has been established that thalassemia is not a single disease but a group of disorders, each of which results from and inherited abnormality of globin production. These conditions form a part of the spectrum of disorders known collectively as the hemoglobinopathies.

The world health organization (WHO) has estimated that each year approximately 2 hundred to 3 hundred (thousands) individual are born with severe hemoglobinopathy, that can be classified in to two types. (1,2,3,5)

DEFINITION

Thalassemia can be defined as a condition in which there is reduced rate of synthesis of one or more of the globin chain leading to imbalanced golobin chain synthesis, defective hemoglobin prouduction and damage to the red cell or their precursors from the effects of globin subunits that are producted in excess. (1,2)

The major defects in red cell maturation and survival which characterize the thalassemias are the direct result of the deleterious effects of these precipitated globin chains.

HEMOGLOBIN

Hemoglobin (Hb), is a complex protein consisting of iron-containing **heme** groups and protein moiety **"globin"** . Hb, is essential to life requires that tissues receive a constant supply of oxygen. The Hb molecule is a tetramer made up of two pairs of polypeptid chains, each chain having a heme group attached. The subunits, α, β, δ, γ, ζ (zeta) and, ε (epsilon), are each convalentlylinked to a heme gtoup. (1,3)

Within the red blood cells of the **embryo, fetus,** and **adult,** six different kinds of Hb may normally be detected;

1- Embryonic Hb	**A- Gower - 1**	$(\zeta_2 \varepsilon_2)$
	B- Gower - 2	$(\alpha_2 \varepsilon_2)$
	C- Portland	$(\zeta_2 \gamma_2)$
2- Fetal Hb	**A- Hb F**	$(\alpha_2 \gamma_2)$
3- Adult Hb	**A- Hb A**	$(\alpha_2 \beta_2)$
	B- Hb A_2	$(\alpha_2 \delta_2)$

The two sets of genes for α and β polypeptid chains are located on chromosomes of 11 and 16.

CLASSIFICATION OF THALASSEMIA

The thalassemia usually classifid two main groups: (4)

1- α thalassemia

2- β Thalassemia

α THALASSEMIA:

Genetic disorders of α chain synthesis result in defective fetal and adult hemoglobin production.

Four genes acompany to making of α.chain, thus one of them or more have disorder or were deleted, results subgroups : (2,5)

A. Silent carrier, hetrozygous α-thalassemia-2 (three α globin genes present $-\alpha/\alpha\alpha$)

B. α-thalassemia triat, heterozygous α-thalassemia-1, homozygous α-thalassemia-2 [$\alpha-$globin genes present: $-\alpha/-\alpha$ or $--/\alpha\alpha$]

C. Hb H disease (one α-globin gene present $-\alpha/--$)

D. hydrops fetalis (no $\alpha-$globin genes present --/--)

E. Hb constant spring (elongated $\alpha-$globin chain α^{cs})

Notes

1- In the fetus a deficiency of α chains leads to the production of an excess of γ-chain which form γ_4 tetramers or **Hb Bart's.** In adult a deficiency of α chains leads to an excess of β chain which form β_4 tetramers or **Hemoglobin H, " Hb H " .**

Thus the presence of hemoglobins Bart's or H are the hallmarks of α-thalassemia. (2)

2- The α-thalassemia has been known for some time that there are two main forms of α-thalassemia; a severe form which produces a typical thalassemia blood picture in heterozygous carriers, and a milder form which is almost completely 'silent' in heterozygotes.

Until recently, the severe form of the condition was called " **α-thalassemia-1** " and the mild form was called " **α-thalassemia-2** " . It is now more usual to call the severe form of α thalassemia " **α^0 thalassemia** " and milder form, " **α^+ thalassemia** ".(2)

β-THALASSEMIA

The β-thalassemia are widely distributed through out the world population and result from a reduction or absence of normal β-globin synthesis. (1,2,3,5)

There are different subgroups of β-thalassemia :

A. **β^+-Thalassemia** (sub optimal β-globin synthesis)

B. **β^0-Thalassemia** (total absence of β-globin synthesis)

C. **$\delta\beta$-Thalassemia** (total absence of both δ- and β-globin synthesis)

D. **Lepore hemoglobin** (total absence of normal δ- and β-globin synthesis with synthesis of small amounts of a fused $\delta\beta$-globin chain)

E. **HPFH** " hereditary persistance of fetal hemoglobin " (reduction or absence of δ- and β-globin synthesis and increased Hb F synthesis)

another classification of β-Thalassemia is :

1- minor β thalassemia

2- intermedia β- thalassemia

3- major β- thalassemia (cooly's animia)

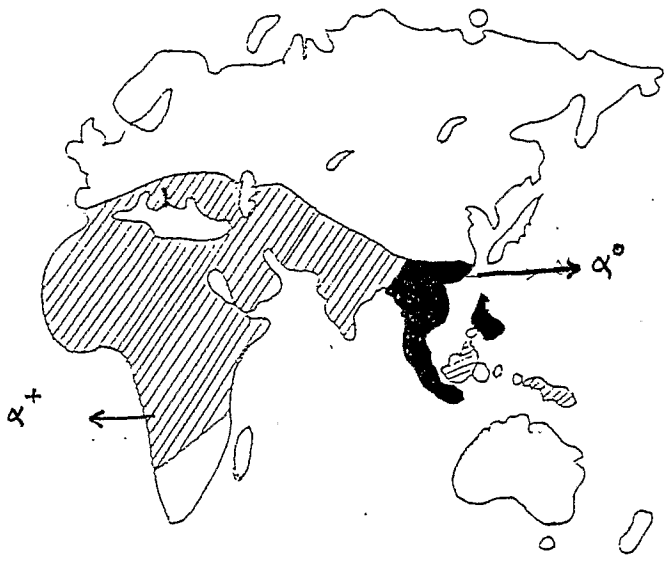
THE α-THALASSEMIA PREVALENCE

The α-thalassemia occur widely throughout Africa, the Mediterranean countries, the Middle East, and South East Asia (Fig 1). The α^0 thalassemia are found most commonly in the Mediterranean and Oriental population and are extremely rare in Africa and the Middle East. However, the form of α^+ thalassemia occur with great frequency throughout West Africa, the Mediterranean, the Middle East, and South East Asia.(1)

Fig 1 : α-thalassemia prevalence

■ α^0-thalassemia

▨ α^+-thalassemia



THE β-THALASSEMIA PREVALENCE

The β-thalassemia are distributed widely among Mediterranean population, in the Middle East, in parts of India and Pakestan, and throughout South East Asia (Fig 2). The disease occurs widely in the Southern parts of the USSR ad in the people's republic of China. The β-thalassemias are much less common in Africa except for some isolated pockets in West Africa notably Liberia and in part of North Africa.

It should be remembered, however, that β-thalassemia occurs sporadically in all racial groups and has been observed in the homozygous state in persons of pure Angle-Saxon stock.

Thus a patient's racial background does not preclude the diagnosis.(1)

Fig 2 : β-thalassemia prevalence

PATHOPHYSIOLOGY

- IMBALANCED GOLOBIN CHAIN SYNTHESIS

- ABNORMAL IRON METABOLISM

- DISORDERED RED CELL METABOLISM

- CONSEQUENCES OF COMPENSATORY MECHANISMS FOR THE ANEMIA OF THALASSEMIA

- IMMUNOLOGIC ASPECT OF β-THALASSEMIA

IMBALANCED GLOBIN CHAIN SYNTHESIS

In homozygous β-thalassamia, β-globin synthesis is either absent or markedly reduced. This results in the production of an excess of alpha-globin chains. (1,2,3,4)

Unpaired $\alpha-$globin chains are incapable of forming a viable hemoglobin tetramer and hence precipitate in red cell precursors. The resulting inclusion bodies can be demonestrated by both light and electronmicroscopy. (1,2,4)

In the marrow, precipitation can be seen in cell throughout the erythroid maturation pathway.

The anemia of β-thalassemia has three major components:

1- most importantly ineffective erythropoiesis

2- hemolysis of circulating mature red cells containing alpha-chain inclusion.

3- reduction in hemoglobin synthesis, resulting in hypochromic and microcytic red cells.