



Epidemiological Characteristics and Disease Complications in Thalassemia Syndrome Patients in Babylon, Iraq

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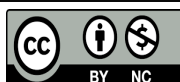
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Article Type	ABSTRACT
Research Paper	<p>Background and Objective: Thalassemia is the most common heritable disorder globally, characterized by the synthesis of low atypical hemoglobin and erythrocytes destruction. There are inadequate data about the epidemiology and other thalassemia traits in Iraq. This study was conducted to inspect the thalassemia epidemiology in Babylon, Iraq.</p> <p>Methods: This single-center retrospective study involved 306 thalassemic patients. Patients were recruited from those recorded at "Babylon Hereditary Blood Disorders Center". Information related to demographic characteristics, age at first diagnosis, socio-economic status, family history, place of residence, frequency of blood transfusions, chelation therapy and serum ferritin measurement were collected and analyzed.</p> <p>Findings: The mean age of the studied patients was 2.3-17.9 years, which included 185 males and 121 females. 75% of the patients had thalassemia major, 12% had thalassemia intermedia, and 0.3% suffered minor thalassemia. 3.3% had thalassemia with G6PD deficiency, 2% had sickle thalassemia, 1.3% had alpha thalassemia, and 4.6% had beta-thalassemia. The patients received regular blood transfusions about once or twice monthly in the majority of the cases (85.6%). The mean serum ferritin concentrations were high (2976.9 µg/L). The growth in the males was affected more than in females ($p=0.05$). Most of the patients were from rural areas and 2/3rd of the thalassemia patients had a family history of thalassemia and a high rate of parental consanguineous marriage ($p=0.001$). The majority of the patients had one or more complications of thalassemia. All the children under 10 years of age included in the study revealed stunted growth significantly.</p> <p>Conclusion: According to the results of this study, the management of thalassemia necessitates early diagnosis of irregular transfusion programs, and associated comorbidities, besides prompt actions. Comprehensive premarital screening, paternal counseling programs, and ongoing regulation can all aid in bringing down prevalence to far lower levels.</p> <p>Keywords: <i>Thalassemia, Prevalence, Demography, Epidemiology, Transfusion, Incidence.</i></p>
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Introduction

Thalassemia is the most common heritable heterogeneous group of disorders globally, characterized by the synthesis of low atypical hemoglobin and excessive destruction of erythrocytes. Thalassemia raised in about 280 million people and resulted in 16,800 deaths in 2015 (1-3). As stated by the World Health Organization report, more than 40000 neonates are delivered with thalassemia annually, of whom around 25500 have hemotransfusion-dependent β -thalassemia (4). Thalassemia affects both sexes similarly and ensues in around 4.4/10,000 live births (5, 6).

There are two categories of thalassemia, based on the mutated globin chain: alpha (α) thalassemia and beta (β) thalassemia. α -Thalassemia arises when one or more genes of α -globin are altered, whereas β -thalassemia arises when both genes of β -globin are altered. Moreover, thalassemia major arises when a neonate receives double parental faulty globin genes, and thalassemia minor arises when the neonates receive one faulty globin gene from one parent only (2). Consanguineous marriage is one of the most described risk factors for thalassemia.

Patients with minor variety display no signs and live a healthy life without medication, whereas those with major variety generally experience permanent anemia, which must be treated with regular blood transfusions (RBT) (7).

Thalassemia patients have long-lasting hemolytic anemia that necessitates RBT from the early years of life (7). The chronic RBT regimen is classically required iron chelators, to avoid the complication of iron overload, including cardiac, hepatic, endocrine, and metabolic dysfunctions (8).

In thalassemia patients, the parameters of physical growth might be normal throughout the first years of life. Thereafter, the majority of the patients fail to achieve the equivalent eventual height as their normal peers (1). Delayed anthropometric parameters are a prominent event with a frequency of 25-66 % universally. Excess iron caused by RBT delays the bony growth and precipitates.

The awareness and the attitudes of the community towards thalassemia have been evaluated by several republics to implement and estimate appropriate educational agendas. Valuation of the people's cognizance of thalassemia recognized that there is a requisite to expand the community's basic understanding of the disease (9).

There are inadequate data about the epidemiology, complications, burden, expenses, and other traits of thalassemia in Iraq, which necessitate further well-designed epidemiological analyses. Therefore, to inspect the epidemiological profile of thalassemia in Babylon province, this study was conducted.

Methods

This retrospective, single-center study involved 306 patients with thalassemia (185 males and 121 females), aged between 2.3-17.9 years. Patients had recruited from those recorded and followed up at "Babylon Hereditary Blood Disorders Center" throughout the period from October 2020 to August 2021.

The total recorded patients in the blood center were 1817 including all varieties of hematological disorders. Those who had a confirmed diagnosis of thalassemia, thalassemia traits or thalassemia varieties were 1151. Our study included a total of 306 based on the following site <https://www.surveymonkey.com/mp/sample-size-calculator/>. The minimum required number was 289 [CI=95%, margin of error=0.05, and population size was 1151].

All patients recorded in the center with a final diagnosis of thalassemia or its varieties, on RBT regimen (regular or irregular), less than 18 years old, and from Babylon province were included in this study. Thalassemic patients who attended the center and were not registered or from provinces other than Babylon,

patients who died, and those with concomitant severe organ failure were excluded from this study. In addition, those with a final diagnosis of hematological disorders other than thalassemia were also omitted.

The identification of thalassemia cases was concluded by the pediatricians and/or hematologists at the center based on history, clinical and laboratory examination and confirmed by hemoglobin electrophoresis. The following data were collected from patients record during their admittance for regular RBCs regimen or follow-up appointments: demographic features; age at first diagnosis, socioeconomic status, family history, residency, frequency of blood transfusions per month, types of chelating therapy, complications; and laboratory results of serum ferritin were taken from patients' records.

All the participants were categorized according to their stature into normal, stunted and severely stunted growth, based on their anthropometrical measurements, which were plotted on CDC and WHO 2007 growth charts for a definite growth evaluation (8).

Ethical approval was acquired from the local hospital ethical committee (BHBDC-2020-12) and Babil Health directorate (BHD-2020-0021). The study was approved by the Institutional Review Board of College of Pharmacy (IRB No. College of Pharmacy 2020-P&T-11). A written agreement was gained from the close relative of the patients.

Statistical data of the patients were collected on Excel worksheet and their analyses were completed employing the SPSS 23. The descriptive quantitative study variables are listed in the form of count +/- percentage, mean, and median +/- SD. A p-value less than 5% reflected significant results in this study.

Results

A total of 306 patients participating in this study were analyzed. Their distribution according to the definite medical diagnosis revealed that the highest number of patients had thalassemia major, followed by thalassemia intermedia (12%) and the lowest was thalassemia minor (0.3%) (Table 1).

Table 1. Distribution of thalassemia syndrome patients according to their definite varieties

Medical diagnosis	Total (n=306) Number(%)
Thalassemia Major	246(80.3)
Thalassemia Intermediate	43(14.1)
Thalassemia Minor	1(0.3)
Sickle thalassemia	6(2.0)
Thalassemia+G6PD	10(3.3)

The main demographic features of thalassemia patients enrolled in the study were shown in (Table 2). The mean age of the included thalassemia patients was 13.0 ± 9.9 (range of 2.3-17.9) years, with significant male dominance (male/female ratio 1.53:1). There was more than one (1.2%) of the children affected by thalassemia syndrome in families that had mean children of around 4%. The patients received regular blood transfusions about once or twice monthly in the majority of the cases. The mean serum ferritin concentrations were high ($2976.9 \mu\text{g/L}$), with non-significant differences in the distribution of patients according to the classes of serum ferritin levels between the sexes. The growth in the males was affected more than in females ($p=0.05$). Most of the patients were from rural areas, however, there were non-significant variations in their socioeconomic status. Two third of the thalassemia patients had a history of thalassemia in their families, and a high rate of parental consanguineous marriage ($p=0.001$). Around two third of the patients were on Exjade iron chelators.

Table 2. Clinical and laboratory parameters of thalassemic children with transfusion-dependent thalassemia (n=306)

Characteristics	Mean±SD or Number(%)	Male Number(%)	Female Number(%)	p-value
Age	13.0±5.9	-	-	
Sex				
Male/Female ratio 1.53:1		185(60.5)	121(39.5)	0.5
Total siblings	3.7±1.7	-	-	
Number Affected sibling	1.2±1.3	-	-	
Transfusion No/month				
Once	138(45.1)	87(47)	51(42.1)	
Twice	124(40.5)	74(40)	50(41.3)	
Thrice	23(7.5)	12(6.5)	11(9.1)	>0.05
Four or more	21(6.9)	12(6.5)	9(7.4)	
S. Ferritin (µg/L)	2976.9	2357.0	2084.3	
<1000	37(12.1)	20(16.5)	17(9.1)	
1000-2000	83(27.1)	38(31.2)	45(24.2)	
2000-3000	71(23.2)	23(19.3)	48(26.1)	>0.05
>3000	115(37.6)	40(33)	75(40.6)	
Weight (kg)	39.7±14.1	-	-	
Height (m)	1.4±0.9	-	-	
BMI (kg/m ²)	18.5±3.2	-	-	
Anthropometric state				
Normal	177(57.8)	107(60.5)	70(39.5)	
Stunted growth	114(37.3)	68(59.6)	46(40.4)	0.05
Severely stunted growth	15(4.9)	10(6.6)	5(3.3)	
Residence				
Rural	188(61.3)	-	-	0.05
Urban	118(38.7)	-	-	
Socioeconomic status				
Enough	75(24.5)	-	-	
Enough to some extent	192(62.7)	-	-	>0.05
Not enough	39(12.7)	-	-	
Family history				
No	116(37.9)	-	-	0.05
Yes	190(62.1)	-	-	
Consanguinity				
Relative	247(80.8)	-	-	0.001
Irrelative	59(19.2)	-	-	
Iron Chelators				
Desferal	112(36.6)	-	-	>0.05
Exjate	194(63.4)	-	-	

The complication of thalassemia was very common, the majority of the patients had one or more complications, which are summarized in Table 3.

Table 3. Complications of thalassemia among studied participants

Complications	No Number(%)	Yes Number(%)
Splenectomy (spleen 1cm below costal margin)	240(78.4)	66(21.6)
Hepatosplenomegaly (liver and spleen 1cm below costal margin)	215(70.3)	91(29.7)
Reaction to blood transfusion	89(29.1)	217(70.9)
Diabetes Mellitus	288(94.1)	18(5.9)
Cardiac complication	284(92.8)	22(7.2)
HIV and HCV infection	289(94.4)	17(5.6)
Hypothyroidism	296(96.7)	10(3.3)
Hypocalcemia	255(83.3)	51(16.7)
Puberty delay	276(90.2)	30(9.8)
Growth failure	268(87.6)	38(12.4)
Joint problem	302(98.7)	4(1.3)
Gallstone	281(91.8)	25(8.2)

All the children under 10 years of age included in the study revealed stunted growth significantly. Those children between the age of 10 and 15 years also revealed delayed growth ($p>0.05$), while the majority of those more than 15 years of age were normally growing ($p=0.001$), (Table 4).

Table 4. Age-wise comparison of height for age z-score (HZS) in children with stunted growth (n=104) vs. normal growing children (n=202)

Age groups (years)	Children with stunted growth (n=104) Height z-score Number(%)	Children with normal growth (n=202) Height z-score Number(%)	p-value
<5	10(100)	0	0.05
5-10	34(100)	0	0.001
10-15	33(61.4)	21(38.6)	0.1
>15	27(12.9)	181(87.1)	0.001

The effects of socioeconomic status of the studied thalassemic patients exposed no significant effects on the study variables (Table 5).

Table 5. Socioeconomic effects on some variables of the study

	Enough Mean±SD	Enough to some extent Mean±SD	Not enough Mean±SD	p-value
Number of affected siblings	1.1±1.029	1.3±1.4	1.1±1.3	>0.05
Frequency of blood transfusion per month	2.1±1.6	2.01±2.2	2.2±2.0	>0.05
Serum ferritin µg/L	3166.6±1876.3	2882.13±2185.3	3018.34±2045.3	>0.05
Total siblings	3.5±1.4	3.8±1.8	3.8±1.7	>0.05
BMI (kg/m ²)	18.6±2.9	18.3±3.5	18.5±2.8	>0.05

The gender of the thalassemic patients in the current study did not reveal significant differences in the variables other than serum levels of ferritin, which was higher significantly among the males. In addition, the incidence of gallstones was more among the male patients significantly ($p=0.04$) (Table 6).

Table 6. Sex variation of the study variables of thalassemic patients

Characteristics	Males Mean±SD or %	Females Mean±SD or %	p-value
Age	13.7±4.35	12.9±4.34	0.2
Serum Ferritin	3172.6±2090	2664.5±1654	0.03
Stunted Growth	56.6%	43.4%	0.9
Splenectomy	56.1%	43.9%	0.4
Hepatosplenomegaly	67.0%	33.0%	0.1
Frequency of transfusion per month	58.5%	41.5%	0.9
Diabetes Mellitus	61.1%	38.9%	0.9
Cardiac complication	68.2%	31.8%	0.4
HIV/HCV	64.7%	35.3%	0.7
Hypothyroidism	60.0%	40.0%	0.9
Hypocalcemia	66.7%	33.3%	0.3
Joint problem	75.0%	25.0%	0.5
Gallstone	80.0%	20.0%	0.04

Discussion

The mean age of the included thalassemia patients was 13.0 ± 9.9 (range of 2.3-17.9) years, with significant male dominance (male/female ratio 15.4:1). Families with history of more affected sibling has more chance to have thalassemia. Most of the patients were poorly controlled as indicated by elevated mean serum ferritin concentrations ($2976.9\text{ }\mu\text{g/L}$). Although both sexes revealed growth impairment, the growth in males was affected more. The majority of the patients were from rural areas, with non-significant variations in their socioeconomic status. There was a high rate of parental consanguineous marriage.

The expected universal prevalence rate of thalassemia is nearly 4.4/10000 according to world health organization (WHO) (10). A previous Iraqi study exposed a prevalence of 37.1/100000 for thalassemia in Iraq. However, in Iraq the prevalence of thalassemia is somewhat growing despite declining incidence (11). Alternatively, several studies in various countries of the world have shown dissimilar prevalence rates. In the United Kingdom, the reported prevalence was 0.3 to 4/1000 (10), in India ranging from 0.1 to 30.4% (12), in Greece 8.0% (13), and 4% to 41% in Italy (14). In the nearby Arabic states; in Iran, the prevalence of thalassemia was 25/100000 (15), in Lebanon the thalassemia carrier rate is 2-3% (16), 2.1% in Turkey (17), and in Saudi Arabia the prevalence was considered one of the uppermost compared to nearby Middle East countries ranging from 0.4% to 5.9% (18).

The recent advances in the management of thalassemia improve the patient's prognostication and survival. During the period from 2010 to 2015, a visible decline in the prevalence of thalassemia in Iraq was reported (11). Nevertheless, hundreds of new patients are born every year in our population. Durable regulations, preventive health measures, and health awareness programs are desirable to further reduce this prevalence to the lowest scores.

Among the numerous varieties of thalassemia, thalassemia major is one of the most common hereditary disorders globally. It is widespread in over 60 countries, with around 150 million carriers all over the world (11). In the current study, the dominant type was thalassemia major. A similar outcome was also observed in several neighboring countries.

The males were more affected than females in the current study, similar to prior studies in Iraq (19, 20) and Pakistan (21). An insignificant variation was observed between the number of male and female thalassemia patients reported in Iran to contradict our findings (22). These variations in the sex prevalence are noteworthy and justify more investigation considering that thalassemia is an autosomal recessive disease and inheritance does not involve the sex chromosome (5, 23).

A closer look at the higher mean levels of serum ferritin doubled the favorite concentrations (1000 ng/dl) among the study patients and reflected a poor control of patients regarding iron overload (2, 3). The unfair control was probably caused by curfew due to COVID-19 conditions during the study, most of the patients from rural areas, and unfortunate socioeconomic status, despite non-significant variation of the socioeconomic among the studied cases. The same explanation can be suggested for the higher rate of prevalence of complications, besides the unavailability of medical facilities at different levels.

Supporting the outcomes of the current study, retarded growth remains one of the most common sequences affecting the life quality of thalassemic patients. The growth retardation in thalassemia is of multiple factors like endocrinopathies, chronic anemia, iron chelators, iron overload, osteoid dysplasia, multi-organ involvement, and others (24).

The prevalence of thalassemia was more among patients descended from rural areas, consistent with the findings of Abdul-Karim et al. in 2005 (20). Families existing in far areas perhaps cannot have the same chance for early management or proper RBT regimen and may die from the disease at an early age. In addition, consanguineous marriage is more common in rural communities. Consequently, one can expect the presence of more than one child affected by thalassemia in one family in this study.

Age-wise comparison of height for age z-score in children with stunted growth compared to normal growing children revealed that the highest frequency of thalassemia was among patients between (1-10) years of age. Supporting our outcomes are two preceding studies (20). These findings can be clarified by the increasing pathology load and reduced life expectancy in thalassemia patients.

The current study also discloses that the frequency of thalassemia was higher in first-order siblings. It is partially suggested that a higher number of thalassemia prevalence in the first birth order could be due to a lack of parental knowledge about the disease's nature and consanguinity. Analysis of the pooled data in the existing study showed that nearly 46.3% of thalassemia families have one affected child, 37.6 % of families have two, and 17.1% have three children with thalassemia. The sizeable number of families having more than one thalassemia child points to the imperfect implementation of preventive measures even for families with a confirmed risk.

The cornerstone element of thalassemia survival is RBT therapy. Nonetheless, it can cause severe problems that may add more to the morbidity or mortality of thalassemia itself, namely, iron overload and transfusion infections (25). In the current study, the frequencies of HBV and HCV infections generally were lower than analogous data from many Arabic countries (26-29). A prior study from the Duhok thalassemia center in north Iraq reported HCV antibodies in up to 56.9% of thalassemic patients (30). Another Iraqi study from Diyala showed a rate of HCV in 26.4% of the patients (31). However, organ enlargement remains the commonest complication in this study.

The management of thalassemia necessitates early diagnosis of irregular transfusion programs, associated comorbidities, and prompt action. Comprehensive premarital screening, paternal counseling programs, and ongoing regulation can all aid in bringing down the prevalence to far lower levels. Due in

large part to the rising rate of marriage in our communities, a successful community-based or national preventive program for thalassemia control is required to safeguard the future generations through special counseling clinics.

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