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Epidemiological and Clinical Profile of Iraqi Patients with β-Thalassemia Major

Ebtissam Yasseen Ali [1] and Maysaloun Muhammed Abdulla[2]

[1] Mb.Ch.B, M.O.H./Al-Najaf
[2] Mb.Ch.B, D.C.M, F.I.C.M.S/CM, Professor, Community & Family Medicine Department/College of Medi cine/Al-Nahrain University. (corresponding author)

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ABSTRACT: *Thalassemia is an autosomal recessive inherited blood disorder due to hemoglobin-production abnormalities. Over the past three decades, hyper-transfusion therapy in these patients has shown significant increase in life expectancy and quality of life. unfortunately, this type of therapy also increased the frequency of complications due to iron overload. The study aims to identify the Sociodemographic and clinical characteristics of patients with thalassemia, and to assess transfusion related complication among them. A descriptive, cross-sectional study was conducted in Thalassemia Center in Al-Najaf province in Iraq, during the period from the 1st of April to the 31st of August 2018. Data were collected through direct interview with patients/parents using a specially designed questionnaire form. A total of 175 transfusion dependent thalassemia major patients were included, the mean age 10. 5 years ranging from 5 m to 34years. Patients under 10 years of age represented the highest rate with Male: Female ratio 1.2:1. 60% were from rural area with high percentage of parental consanguinity (70%). The study documented the relationship between iron over load and appearance of complications. Development of preventive measures as genetic counseling, prenatal diagnosis, pre-marital screening are the best ways to decrease the incidence of disease, in addition to regular blood transfusion with optimum chelation therapy.*

KEYWORDS: thalassemia, epidemiology, anaemia.

INTRODUCTION

Thalassemia syndromes refers to a spectrum of diseases characterized by reduced or absent of one or more globin chain. Thalassemia was not recognized as clinical entity until 1925 where Cooley and Lee described a syndrome occurring in children of Italian origin and associated with splenomegaly and bone change[1]. Mutations in the beta-globin gene cluster occur at high frequencies (>1%) in regions including the Mediterranean, Middle East, northern Africa, India, and almost all of Southeast Asia[2]. Although the prevalence of these mutations is low in the populations of northern Europe and North America, widespread immigration has led to worldwide distribution. [3, 4, 5]

There is a little data on epidemiology and burden of thalassemia in Iraq. Thalassemia represented 75% of all hemoglobinopathies in Iraq and beta- thalassemia major represent 67% of all type of thalassemia[6].

A variety of mutations in the gene or its regulatory elements cause defects in the initiation or termination of transcription, abnormal RNA splicing or cleavage, substitutions, and frame shifts. The result is decreased or absent production of beta-globin chains, giving rise to the beta-thalassaemia syndromes. The underlying pathophysiology of beta-thalassaemia syndromes is ineffective erythropoiesis. In beta-thalassaemia major there is a complete or near-complete lack of beta-globin, leading to a transfusion-dependent severe anaemia[7].

Thalassaemia may be classified into Genotypic classification; Heterozygous beta-thalassemia (beta-thalassemia trait) and Homozygous beta-thalassemia,[8] and Phenotypic classification; Silent carrier, B Thalassemia minor, β Thalassemia intermedia and β Thalassemia major[1,9,10, 11]. The severity of the clinical manifestation and laboratory findings in thalassaemia largely depends on the genotype. Thalassaemia major (Cooley's anemia) patients develop a severe, life-threatening anemia during their first year or two of life. To survive childhood, they require chronic transfusion therapy to correct their anemia and suppress their high level of ineffective erythropoiesis. Beta-thalassaemia major and intermedia are genetic conditions associated with significant morbidity and a decreased life expectancy[12, 13, 14, 15]. All women at risk for being carriers, based on family history or ethnic background, should be antenatal screened by blood counts and haemoglobin analysis, and should be offered antenatal diagnosis and genetic counseling[16].

The average rate of Hb fall in patients is with thalassemia major is 1g/dl per week. regular blood transfusion usually administered every two to five weeks to maintain the pretransfusion hemoglobin level above 9 – 10.5 g/dl. Doing so can cause a high amount of iron to build up in the body, which can be harmful. Persons who receive significant numbers of blood transfusions need a treatment called chelation therapy to remove excess iron from the body[11] Deferoxamine (Desferal) is given 5–6 days a week at a dose of 20-40 mg/kg/day[11, 12]. Deferasirax (Exjade) is an orally active chelator that is highly selective for iron, Promotes excretion of iron in the feces. The recommended initial dose of Exjade is 20 mg/kg bodyweight once daily[12] and Deferiprone is a new iron chelator used for children >2 year of age. Adverse effects of deferiprone include agranulcytosis, arthropathy which necessitates discontinuation of the therapy. Gastrointestinal intolerance, zinc deficiency and fluctuation of liver enzymes are other side effects[17]. Thalassemia is often accompanied by the destruction of a large number of red blood cells, and the task of removing these cells causes the spleen to enlarge[13]. Severe enlargement of the spleen more than 6cm below the costal margin and the presence of leucopenia or thrombocytopenia may necessitate its removal. splenectomy can have serious consequences, including infection, pulmonary hypertension, and thrombosis . the patient should be fully immunized against encapsulated bacteria before splenectomy and subsequently should be on long term penicillin prophylaxis[12, 14].

All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation in which substitution normal stem cells for stem cells harboring defective globin

genes. It offers the only cure available for B-thalassemia major, should be considered for patients at an early age (children younger than 15 years of age) or before complications due to iron overload have developed[15]. In gene therapy; the bone marrow of patient is harvested and beta globin gene is incorporated into stem cells and reinfused in the body system. This is done by transfer of recombinant DNA into human cells for correction of disease. There are viral and non-viral vectors for gene expression[15]

Blood transfusions can result in too much iron, which can damage the heart, liver, and endocrine system. Less. Early recognition and prevention of the endocrine complications, by early and regular chelation therapy, is mandatory for the improvement of the quality of life and psychological outcome of these patients[18]. Patients with multi-transfused thalassaemia major may develop severe endocrine complications due to iron overload. The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion resulting in hypogonadism, short stature , acquired hypothyroidism and hypoparathyroidism. Glucose intolerance and diabetes mellitus are also common in thalassemic patients[19]. Monitoring should be performed regularly for the following complications; 1)Iron load, Consistent rising serum ferritin levels or intermittent transfusions given at a volume likely to require chelation[20] 2) Cardiovascular by Cardiac MRI annually, 3) Hepatobiliary by Holter monitoring annually, 4) Bilirubin levels and AST/ALT monitoring at each transfusion visit if on deferasirax or if active hepatitis B virus or hepatitis C virus infection; less frequently if on desferrioxamine, 5) Hepatitis B virus and hepatitis C virus serology annually, 6) Renal monitoring for Urea and serum creatinine at each transfusion visit if on desferrioxamine or deferasirax, 7) Endocrine, for Thyroid and parathyroid function annually, 8) monitoring for Bone density, Glucose tolerance, HIV serology, Vision and hearing are done annually, 8) HCG, testicular, and ovarian function monitoring is based on age and clinical indication while Pulmonary function is monitored every 2 years[21].

Life expectancy of Beta-thalassaemia trait has no difference from normal[22].While Beta-thalassaemia intermedia may have significant cosmetic changes in appearance which may interfere with quality of life, Beta-thalassaemia major; If untreated, is usually fatal in the first few years of life, death being the result of heart failure secondary to severe anaemia[23].
The aim of this study is to determine the Sociodemographic characteristics and to assess the clinical aspects of beta- thalassemic major blood transfusion dependent patients at thalassemia center in Al-Zahraa hospital at Al-Najaf governorate.

PATIENTS AND METHODS

A cross sectional study was performed at Thalassemia center in Al-Zahraa Hospital at Al-Najaf province/Iraq, this center contains four wards, it affords services for about one thousand of patient with different types of hemoglobinopathies and all the patients receive different types of health care services such as counselling and management especially blood transfusion . The study was conducted for the period from April 1st to August 31st 2018, three days a week and four hours per day. A convenience sample of B Thalassemia patients attending Thalassemia Centre during the study period was selected. Data were collected through direct interview with patients/parents and

from patients' records using a pre tested structured questionnaire form which was specially designed for this study. Only thalassemia major patients with blood transfusion were included.

Data collected were related to; sociodemographic characteristics such as age (in years), gender (male or female), residence (urban or rural) and parental consanguinity, in addition to information about B thalassemia which consisted of; age at diagnosis and the age at first blood transfusion in years; classified into 4 categories (under 1 year, 1- <2 years, 2- <3 years and 3+ years), Interval of blood transfusion in weeks, type of transfused blood cells (filtered blood cell or non-phenotypically RBC), Chelation history such as; age of first chelation and type of chelating agent (Deferoxamine, Deferasiraox, or Deferiprone), History or presence of infectious disease due to blood transfusion such as Hepatitis B, Hepatitis C, and HIV.

Serum ferritin level was estimated for all patients in this study which was grouped into 4 categories; 1001-1500 ng/ml, 1501-2500 ng/ml, 2501-5000 ng/ml, and >5000 ng/ml). Other variables included were; History of splenectomy (as a treatment for B thalassemia), vaccination after splenectomy, type of vaccination, type of prophylactic antibiotics, and Complications associated with B thalassemia whether cardiac, endocrine or other complications.

The study protocol was reviewed and approved by scientific committee at Family and Community Medicine Department at Alnahrain college of Medicine. Approval and official permissions were obtained from; the Iraqi Board of Medical Specialties, and Al-Najaf Health Office and Administration of Al-Zahraa Hospital and Thalassemia center.

All participants were given enough information, in a way they can understand, about the potential benefits of being involved in study and that information obtained would be confidential. A verbal consent from each participant/parent was obtained prior to the start of data collection.

Data of the studied group were entered and analyzed by using the statistical package for social sciences (SPSS) version 23. Descriptive statistics were presented as frequencies, proportions (%), means and standard deviation (SD). Chi square test was used to estimate the association between two categorical variables. Level of P value < 0.05 was considered as significant.

A pilot study was carried out on a sample from thalassemia center consisted of twenty B thalassemic patients selected randomly and interviewed. Those patients were not included in the current study. The purpose of the pilot study was to assess the feasibility of questionnaire and the time required for each interview, and to find out if there would be any difficulty/obstacle to conduct the study, so that possible change or correction to the questionnaire could be made accordingly.

RESULTS:

A total of 175 patients with thalassemia major were included in this study. Mean age ± SD (10.5 years±5.8 years) and the range from 5 months to 34 years, 94(54%) were males and 81(46%) were females with a ratio 1.2: 1 (figure 1).

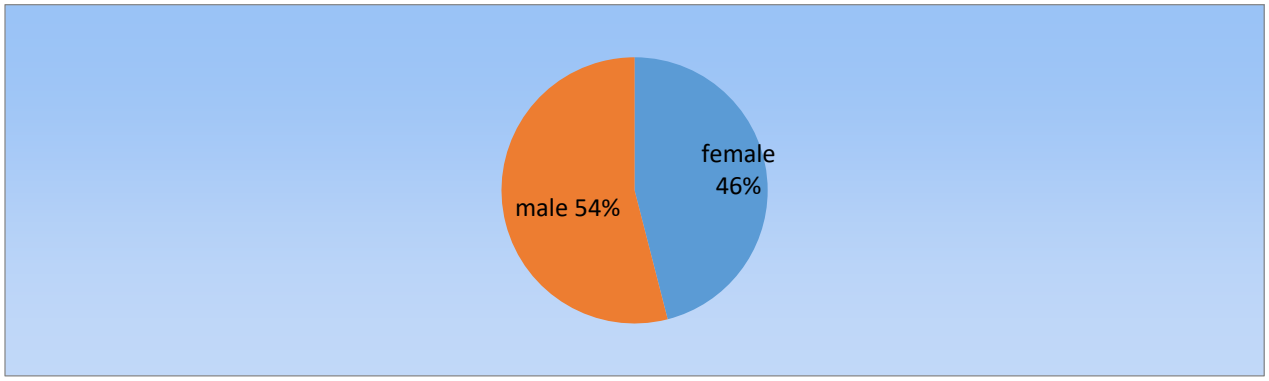

Figure 1: Distribution of thalassemia major patients according to sex (N= 175).

more than half (55%) aged 1 to 10 years. The highest rate (60%) of patients were from rural areas. Parental consanguinity, of different degrees, was positive in 70% (110) of cases. 81 (46.2%) patients were diagnosed as thalassemia in their first year of life and age at diagnosis of 36 (20.5%) patients was after 3 years of age (Table-1).

Table-1: Distribution of patients with thalassemia major according to Sociodemographic characteristics.

Sociodemographic characteristics	Frequency (%)
Mean age ±SD	10.5 years±5.8
Range	(5 months - 34 years)
Age group(years)	
<1years	12(6.85%)
1-5years	44(25%)
> 5-10years	54(30.8%)
>10 years	65(37%)
Age of diagnosis	
<1 year	81(46.2%)
1 - 2 years	29(16.5%)
2- 3years	29(16.5%)
3+years	36(20.5%)
Residence	
Urban	70(40.2%)
Rural	105(60%)
Consanguinity	
Yes	110(70%)
No	65(30%)
total	**175**

Majority of patients (72.6%) had blood transfusion at 3-4 weeks interval, while on emergency transfusion was found in only 4% of the study sample. Type of transfused blood cells was filtered blood cells in about 79.4% (139) of patients while the rest 36 (20.5%) received non phenotypically red blood cells. Transfusion-transmitted infection was found among 7 (4 %) patients; Hepatitis B (2.2%) and Hepatitis C (1.7 %) viral infections, while no HIV infection was detected (Table 2).

Table-2: Distribution of thalassemic major patients according to blood transfusion characteristics.

Blood transfusion characteristics	Frequency(%)
Transfusions Interval	
3-4 weeks	127(72.6%)
5-6 weeks	27 (15.4%)
7-8 weeks	14 8%)
On emergency	7 (4%)
Type of transfused blood cells	
Filtered blood cells	139 (79.4%)
Non-phenotypically RBC	36 (20.5%)
Transfusion transmitted infection	
Hep B	4 **(**2.2%)
Hep C	3 (1.7%)
HIV	0(0.0%)

Chelation therapy was administered to 156 (89%) patients, the age of first chelation in 39.7% of them was before 3 years of age while the rest (approximately 60%) had it at the age of 3 years and above. Deferoxamine was the most commonly used iron chelator 92(52.6%), Table-3.

Table-3: Distribution of thalassemic major patients according to chelation therapy and ferritin level.

Variables	Frequency (%)
Age of first chelation (N=156)	
<3 years	62 (39.7%)
3+	94 (60.3%)
Type of chelation therapy(N=156)	
Deferoxamine	92(52.6%)
Deferasirax	43(24.6)
Deferiprone	21(12.8%)
Serum ferritin level (N=175)	
<1500	41 (23.4%)
1500-2500	64 (36.5%)
2501-5000	52(29.7%)
>5000	18 (10.4%)

Serum ferritin level was done for all patients participated in this study and the results were as fellow; 41 patients(23.4%) had serum ferritin level between 1001-1500ng/ml, a moderate iron overloud between 1501-2500ng/ml was found in 64 patients (36.5%), 52 patients (29,7%) between 2500-5000ng/ml ,while those with a level above 5000 ng/ml was 18 patients (10%) only (Table-3).Splenectomy was done for 63 (36%) patients and the mean age of splenectomy was 8.3 years ±2.5.(figure 2).

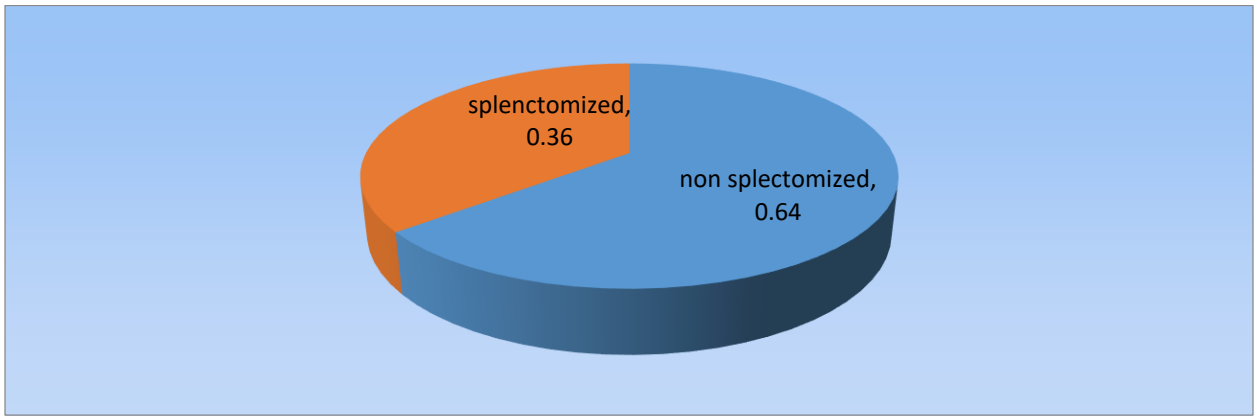

Figure-2: Distribution of thalassemic patients according to splenectomy

Thalassemic patients at thalassemia center were vaccinated against multiple microorganisms such as; streptococcus pneumonia (87.4%), H. Influenza type b (77 .2%) and Neisseria meningitis (80.6%), (Table-4). Prophylactic antibiotics which were administered to splenectomized patients either Benzathin penicillin (55.8%) or oral penicillin (40%), (Table-4).

Table-4 distribution of thalassemia major patients according to vaccination and prophylactic antibiotics

Variable	Frequency (%)
Vaccination (N= 63)	
Type of vaccination	
Streptococcus pneumonia	55 (87.4%)
H influenza type b	48(77.2%)
Neisseria meningitis	51(80.6%)
Prophylactic antibiotics (N=63)	
Types of antibiotics	
Benzathin-penicillin	44 (69.84%)
Oral penicillin	19 (30.16%)

The rates of complications among transfusion dependent patients in the current study were as follow; 16% (28) of all patients had cardiac problems (arrhythmia 3 (10.7 %), heart failure 18 (64.2 %) and pulmonary hypertension 7 (25 %) patients), figure-3, endocrine disorders such as delayed puberty in 56 (32%) patients, Growth retardation in 19 (10.8%) patients, Thyroid disorders in 5.1% (9 cases) of patients, and Diabetes mellitus was seen in 6 (3.4%) cases (table 5). The association of different complications with; blood transfusion intervals and serum ferritin level among patients with thalassemia, are shown in tables 6 and 7 respectively.

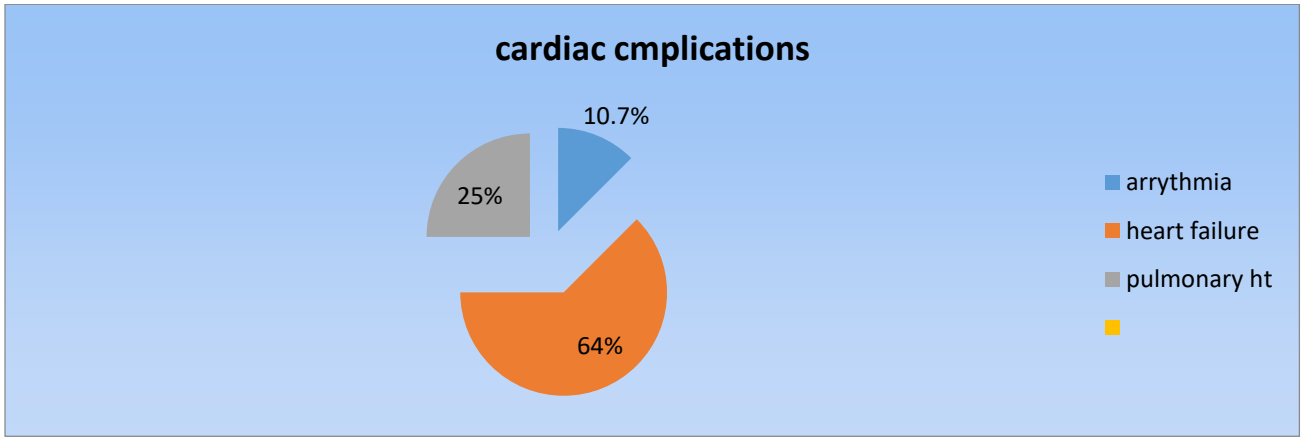

Figure 3:Types of cardiac disorders among Patients with thalassemia major (N=175).

Table-5: Distribution of patients with thalassemia major according to endocrine complication .

Endocrine complication	Frequency (175)(%)
Delayed puberty	56 (32%)
Growth retardation	19 (10.8%)
Thyroid disorder	9 (5.1%)
Diabetes mellitus	6 (3.4%)

Table-6: Distribution of patients with thalassemia major according to complications by transfusion interval.

complication	Blood transfusion interval					
	3-4 week	5-6 week	7-8 week	On emergency	Total	P value
Cardiac **Yes** **no**	11(6.3%) 116(66.3%)	9(5.1%) 18(10.3%)	5(2.9%) 9(5.1%)	3(1.7%) 4(2.3%)	28(16%) 147(84%)	0.001
Delay puberty **Yes** **No**	25(14.3%) 102(58.3%)	17(9.7%) 10(5.7%)	11(6.3%) 3(1.7%)	3(1.7%%) 4(1.3%)	56(32%) 119(68%)	0.001
Growth Retardation **Yes** **No**	9(5.1%) 118(67.4%)	5(2.9%) 22(12.6%)	4(2.3%) 10(5.7%)	1(0.6%) 6(3.4%)	19(10.8%) 156(89.1%)	0.043
Thyroid dysfunction **Yes** **No**	6(3.4%) 121(69.1)	2(1.1%) 25(14.3%)	1(0.6%) 13(7.4%)	0(0.0%) 7(4%)	9(5.1%) 166(94.8%)	0.829
Diabetes **Yes** **No**	3(1.7%) 124(70.8%)	1(0.6%) 26(14.8%)	1(0.6%) 13(7.4%	1(o.6%) 6(3.4%)	6(3.4%) 169(96%)	0.318

Table 7: Distribution of patients with thalassemia major according to endocrine complications by serum ferritin level.

Endocrinopathy	Total number	Ferritin level <1500	1500-2500	2501-5000	>5000	P value
Delayed puberty Yes No	56 (32%) 119 (68%)	7 (4%) 34 (19.4%)	9 (5.1%) 55 (31.4%)	23 (13.1%) 29 (16.6%)	17 (9.7%) 1 (0.6%)	0.0001
Growth retardation Yes	19 (10.9%)	5 (2.9%)	4 (2.3%)	6 (3.4%)	4 (2.3%)	0.4288

No	156 (89.1%)	36 (20.8%)	60 (34.3%)	46 (26.3%)	14 (8%)	
Thyroid disorders Yes	9 (5.14%)	2 (1.1%)	2 (1.1%)	3 (1.7%)	2 (1.1%)	0.5942
No	166 (94.8%)	39 (22.3%)	62 (35.4%)	49 (28%)	16 (9.1%)	
Diabetics Yes	6 (3.4%)	2 (1.1%)	1 (0.6%)	2 (1.1%)	1 (0.6%)	0.5680
No	169 (96.6%)	39 (22.3%)	63 (36%)	50 (28.6%)	17 (9.7%)	

DISCUSSION

Thalassemia major happen when a child inherits two mutated genes from father and mother. Children born with this disease usually develop severe anaemia during their first year of life. They lack the ability to produce adult Hb, consequently this will lead to growth retardation, impaired physical activities, bone changes and enlargement of liver and spleen. The only treatment to correct anaemia is regular blood transfusion and chelation therapy[1].

A slight male predominance was found in this study with a male to female ratio of 1.2:1 which is in agreement with similar studies carried out by Zamani et al in Iran and in Tunisia which revealed percentage of males 54.9% and 55.4% respectively[24, 25]. A similar sex ratio was found in a study conducted in Bangladesh in 2017,which reported a male to female ratio of 1.14:1[26].

The mean age among thalassemic patients in the current study was 10.5 years and range 5 month-34 years, similar to that reported by Bejaoui and Gurrat (10.7 years) in Tunisia[25]

In contrast to our study, a comparatively higher mean age of thalassemic patients was shown in Iranian cohort in 2013 (15.2 years) and United Arab Emirates study (15.4 years)[24, 27], and a much higher in North America (20 years)[28, 29]. This could be explained by late detection of the disease in Iraq because of low level of community awareness of the disease and fewer available facilities to seek medical advice. On the other hand, lower mean age was reported in India in 2016[30]. Half of thalassemic patients in this study were first diagnosed during their first year of life, similar to a study carried out in India[30]. Modell and Berdoukas[31] reported 60% of their patients had presented clinically in the first year of life.

The prevalence of thalassemia major is high in countries where there are relative marriages. Geographic distribution in this research found that majority of thalassemia major patients are from rural areas where relative family marriages commonly occur[32]. Our result is in agreement with a study done in Iran[24], but differs from that shown in the Lebanese study in which thalassemia was homogeneously distributed all over the country[33].

Positive parental consanguinity was found in 70% of all studied patients, this may be explained by the fact that thalassemia is transmitted as an autosomal recessive type. A comparably high consanguinity rate was estimated in the Iranian study[24] and a study in Tunisia[25]. One of the reasons for high rate of parental consanguinity among thalassemic patients could be lack of knowledge and awareness about the risk of thalassemia following familial marriage[26].

Blood transfusion and chelation therapy remain the cornerstone of treatment of thalassemia major[34]. There are several risks due to chronic blood transfusion like; infection, iron overload because of repeated blood exposure[35].

A High percentage of patients receiving chelation therapy 89% (156**)** was reported in current study, similar to a study done in Tunisia[25]. A comparably lower percentage 40% was reported in Bangladesh in 2017[26].

The optimal time for initiating iron chelation therapy in patient with thalassemia remains uncertain, in theory it should start as early as possible to prevent complications. Federation recommended that chelation initiated when serum ferritin levels reach approximately 1000ng/ml, which usually occurs after the first 10-20 transfusions or around 2-3 years old[36, 37], in this study the rate was 39.7% under 3 years. The delay age of initiation of chelating therapy is related to literacy (ignorance) hence the delay in seeking medical advice until complication appearance [36, 38].

Iron over load associated endocrine complication were reported in 60% of chronically transfused thalassemia major patients with a dysfunction of at least one gland[39, 40] , these include delayed puberty, growth retardation thyroid disorder and diabetes mellitus.

Delayed puberty is the most common complication in this study, a finding consistent with Italian cohort in which hypogonadism was reported in 50% of patients[41] while prevalence of growth retardation (26.7%) was higher than that repotted in Italy (5%)[42], hypothyroidism, diabetes mellitus and hypo parathyroidism were estimated particularly among patients in their second decade of life. No significant association was identified between serum ferritin level and diabetes mellitus among thalassemia patients in the current study.

Splenectomy is beneficial in treating thalassemia major, it decreases patients transfusion requirements and increases the mean level of hemoglobin[18]. 36% of our patients underwent splenectomy and this may indicate that previous transfusion therapy had been inadequate in at least some of them. There is a risk of invasive bacterial infections supported by data collected by Bisharat et al.[19].Thus prevention and treatment of bacterial infection are life saving measure,

splenectomized cases should receive routine vaccination including both live attenuated and killed vaccine but they should also be vaccinated against Streptococcus pneumonia, H.influenza type b, and Neisseria meningitides. In addition to administration of prophylactic antibiotics to complete protection against infection with encapsulated bacteria[19].

The goal of transfusion is to shut off erythropoiesis as much as possible. Transfusions should be scheduled in advance and maintained at a fixed schedule. This enables patients and families to establish routines and will improve quality of life.

The recommended treatment for thalassaemia major involves lifelong regular blood transfusions, usually administered every two to five weeks, to maintain the pre-transfusion haemoglobin level above 9-10.5 g/dl. This transfusion regimen promotes normal growth, allows normal physical activities, adequately suppresses bone marrow activity in most patients, and minimizes transfusional iron accumulation.

This study showed a relation between blood transfusion intervals and cardiac complications. Iron overload was found to be associated with endocrinopathy such as delayed puberty and growth retardation which were frequently reported complications among chronically transfused patients and have relation with infrequent blood transfusion. Blood transfusion intervals in patients with thalassemia major who have some endocrine complications (diabetic mellitus and thyroid dysfunction) were not significantly different from those without those complications. Although shorter intervals between blood transfusions may reduce overall blood requirements, the choice of interval must take into account other factors such as the patient's school or work schedule and other lifestyle issues.

CONCLUSIONS

The highest rates of B thalassemic patients were; under 10 years, males, from rural areas with high percentage of parental consanguinity. Most blood transfusion dependent patients were regularly transfused, chelation therapy was administered to majority of patients with deferoxamine as the most commonly used iron chelator. The majority of patients had high serum ferritin level which was associated with multiple complications such as cardiac and endocrine problems and one third were underwent splenectomy. Most of the patient in current study received vaccination and prophylactic antibiotics.

Development of preventive measures as genetic counseling, prenatal diagnosis, pre-marital screening are the best ways to decrease the incidence of disease, in addition to regular blood transfusion with optimum chelation therapy including optimum age of starting of chelation dose and frequency per week. Health education about thalassemia by periodic sessions for targeted groups should be done as a strategy to increase the awareness about the mortality and morbidity specifically of transfusion dependent thalassemia major patients who should do regular routine investigations and monitoring of iron status by serum ferritin level to prevent complications and decrease the burden of the disease.

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