SCREENING FOR BETA THALASSEMIA AMONG THE RELATIVES OF B. THALASSEMIA PATIENTS

By

Ali Abd El-Latif Afia*, Mohamed Saeed El-Shorbagy, Ali Mohamed Shaaban***

Pediatrics* and Clinical Pathology** Departments, Faculty of Medicine, Al-Azhar University

Corresponding Author Name: Ali Mohamed Shaaban,

Mobile: 01026786652, **E-mail:**

ABSTRACT

Background: *Thalassemia is recognized as the most prevalent hereditary disorder all over the world with a significant negative impact on public health and the society especially endemic areas. In Egypt, The most prevalent hemoglobinopathy is β-thalassemia major. It is considered a major health problem in our region. Prevention by carrier detection and prenatal diagnosis is needed in populations with high incidence of the disease. The aim of the present work was to screen for beta thalassemia among the relatives of B thalassemia patient.*

Methods: *This study was carried on 100 children, aged (1.5-12) years old with mean 6.4± 2.6 years that were subjected to the following: Detailed history taking. Thorough clinical examination, Laboratory investigations: Complete Blood Count: The key components of the CBC include: hemoglobin, RBC count, mean corpuscular volume HbA2 Estimation.*

Results: *The results of complete blood count testing of all studied subjects revealed that (43%) subjects were non anemic, (57%) subjects were anemic. Among anemic group, (13%) subjects had normocytic anemia and (30%) subjects had microcytic anemia. Microcytic anemia group were further divided into two groups according to HbA2 level, B-thalassemia carrier group (with HbA2>3.5) were (10%) and non-thalassemia carrier group (with HbA2<3.5) were (90%). This study showed that, non-statistically significant deference between cases with B-thalassemia and without regarding sex and age.*

Conclusion: *Carrier rate among 100 relatives of B thalassemia patient was 10% Prevalence of microcytic anemia among the studied group was 30%.Carrier rate among the microcytic anemia group was 33.3% depending on the level of HbA2.*

Key words: *Beta Thalassemia, relatives, Screening.*

INTRODUCTION

Thalassemia is recognized as the most prevalent hereditary disorder all over the world with a significant negative impact on public health and the society especially endemic areas **(Gumuş P, Kahraman-Çeneli S, et al., 2016)**.

In Egypt, The most prevalent hemoglobinopathy is β-thalassemia major. It is considered a major health problem in our region **(Zahran AM, Elsayh KI, et al., 2016)**.

Prevention by carrier detection and prenatal diagnosis is needed in populations with high incidence of the disease. Several prevention programs have been applied in at risk populations in the Mediterranean areas **(ElBeshlawy A, ElShekha A, et al., 2012)**.

A major outcome of thalassemia screening is a reduction in the incidence of thalassemia. The other factors that can lead to a reduction in disease incidence is the prenatal diagnosis and use of reproductive technologies to prevent the births of affected children, as well as a decrease in marriages between carriers **(Cousens NE, Gaff CL,et al., 2010)**.

- Submission date: 1/11/2020.

- Acceptance date: 16/12/2020.

In Egypt, Beta-thalassemia creates a social and financial burden for the patients' family and the Egyptian government. The high frequency of β-thalassemia carriers with increasing rate of newly born cases is a pressing reason for the importance to develop prevention program for β-thalassemia in Egypt **(ElBeshlawy A, ElShekha A,et al., 2012)**.

Community screening is an important component of identifying carriers in the country. Whether carrier screening should be done at school or college level, before or after marriage or during pregnancy is debatable **(Sangkitporn S, Sangnoi A, et al., 2005)**.

The experience of other countries with a high health burden due to thalassemia suggests that the birth rates of patients with β-thalassemia major may be significantly reduced by widespread screening and education programs **(Jameela S, Sabirah SO, et al., 2011)**.

The aim of the present work was to screen for beta thalassemia among the relatives of B thalassemia patient.

Ethical Considerations:

- The study was done after approval of ethical committees of Pediatrics department, Al

Hussein hospital, faculty of Medicine, Al-Azhar University.

- A written consent was taken from all parents before children getting involved in the study.
- Confidentiality of all data was insured.
- The parents have the right to withdraw from the study at any time without giving any reasons.
- The author didn't receive any financial support for the study on publication.
- The author declared that there is no conflict of interest regarding the study on publication.

PATIENTS AND MATERIALS

Inclusion criteria:

1. First degree relatives (siblings).
2. Age: from 1.5 year to 12 year.

Exclusion criteria:

1- Age: less than 1.5 years and more than 12.5 years.

- Increased RDW value in CBC more than normal value < 16.5 **(Irwin JJ, Kirchner JT. Anemia in children. Am Fam Physician. 2001)**.

This study was carried on 100 children, aged (1.5-12) years old from Al-Hussein university hospital, Sayed Galal university hospital and Damanhour medical national institute during the period from 9/2018 to 12/2019. They were selected by simple random method.

They were subjected to the following:

I. Detailed history taking.

II. Thorough clinical examination.

III. Laboratory investigations including:

A. Complete Blood Count: by automated hematology analyzers.

B. HbA2 Estimation: by red cell indices are confirmed for carrier state by HbA2 measurement using the hemoglobin analyzer ARKRAY ADAMS A1C HA-8180T (Japan device) **(Galanello R and Origa R 2010)**.

C. Serum iron level by automated analyzer.

D. Total iron binding capacity (TIBC) by automated analyzer.

E. Serum ferritin: using Tosoh AIA1800ST (Japan) immunoassay analyzer.

Lastly, we classified our studied patient into 2 groups:

- **Group I:** Non anaemic (normal) group (Hb level was normal according to age) **(Irwin JJ, Kirchner JT. Anemia in children. Am Fam Physician. 2001)**.
- **Group II:** Anaemic group, depending on the full criteria for diagnosis of anaemia:
  - HB Level was less than normal range according to age 1.5 years to 12 years.
  - HCT Level was less than normal range according to age 1.5 years to 12 years.
  - MCV Level was less than normal range according to age 1.5 years to 12 years **(Kilpatrick GS, Hardisty RM, 2005)**.

Statistical Analysis:

The data were coded, entered and processed on computer using Statistical package for social science (SPSS) (version 24).The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency, and percentage were used as descriptive statistics. The following test was done: Chi-Square test X^2 was used to test the association variables for categorical data. Student's-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. P value was considered significant as the following: $P > 0.05$: Non-significant. $P \leq 0.05$: Signifstorag.

RESULTS

Table (1): Demographic data of the studied cases (sibilings)

Variable	**(n=100)**	
Age: (year) Mean ± SD Range	 6.4± 2.6 1.5 – 12	
Variable	**No**	**%**
Sex: Female Male	 40 60	 40% 60%
Residence : Rural Urban	 84 16	 84% 16%
Family History: **+ve Consanguinity** **-ve Consanguinity**	 12 88	 12% 88%

This table shows that the age of the studied group ranged from 1.5 to 12 years with mean 6.4± 2.6 years. Regarding sex 60% of them were male and 40% were females.

Table (2): Complete blood count of all the studied subjects

	Variable	**(n=100)**
RBCs: ($x10^6/mm^3$)	Mean ± SD Range	4.38± .432 3.40 – 5.50
Hb: (gm/dl)	Mean ± SD Range	12.04± 1.53 8–14.9
HCT: (%)	Mean ± SD Range	37.17± 4.47 27–46.5
MCV: (fl)	Mean ± SD Range	82.80± 6.95 63–92
MCH: (pg)	Mean ± SD Range	26.96± 2.58 17.7 – 32
MCHC: (%)	Mean ± SD Range	31.50± 1.60 27.5–35.7
RDWcy: (%)	Mean ± SD Range	14±1.68 9.5 – 17.6
WBCs: ($x10^3/mm^3$)	Mean ± SD Range	7.27± 1.65 4.2 –11.5
Platelets: ($x10^3/mm^3$)	Mean ± SD Range	284.86± 109.97 90–480

This table shows that CBC within normal range

Table (3): Serum level of Serum Ferritin (ug/l), Serum Iron(µg/dl) and TIBC(µg/dl)

Variable		Non carrier HbA2<3.5 (n=20)	Carrier HbA2>3.5 (n=10)	t	P
Serum Ferritin (ug/l)	Mean ± SD Range	7.30± 2.92 4-14	88.14± 9.81 75-97	-2.13	.001
Serum Iron (µg/dl)	Mean ± SD Range	33.80± 4.95 25-40	79.32± 3.37 70-84	-1.69	.011
TIBC(µg/dl)	Mean ± SD Range	562± 35.41 500-620	260.42± 44.20 180-280	3.38	.004

This table shows that there were statistically significant differences between thalassemia carriers and non- carrier among microcytic anemic group as regards serum ferritin, serum iron, TIBC.

Table (4): Classification of all the studied subjects from CBC

Total (n=100)		
Non anemic (n=43)*	**Anemic (n=57)****	
43 (43%)	Normocytic anemia MCV >80fl n=13 (13%)	Microcytic anemia MCV<80 fl n=44 (44%)

** Less than normal level of HB, HCT and MCV for age

This table shows that 57 cases were anemic, 13 cases of them were normocytic anemia and 44 cases were microcytic anemia.

Table (5): Result of screening among the studied group

Variable	(n=30)	
	No	**%**
Non-carrier (HbA2<3.5)	80	80
Carrier (HbA2 >3.5)	17	17
B-Thalassemia intermedia HbA1:83.7 % HbA2: 3.6 % HbF: 12.7%	1	1
B-Thalassemia major **Case 1** HbA1:0.6 % HbA2: 4.7 % HbF:94.7% **Case 2** HbA1:0.7 % HbA2: 4.8 % HbF:94.5 %	2	2
Total	100	100.0

This table shows that 17% were B.Thalassemia carrier, 2% were B.Thalassemia major, 1% were B.Thalassemia intermediate and 80% non-carrier (microcytic hypochromic anemia due to iron deficiency anemia.

DISCUSSION

This study was carried out on children, aged (1.5-12) years old with mean 6.4± 2.6 years who attended to clinic of pediatric department Alhussein Hospital, Sayed Galal Hospital and Damanhour medical national institute. During the period from 9/2018 to 12/2019.

Our results showed that (60%) of them were males and (40%) were females, (84%) rural and (16%) urban.

These results disagree with **Abozaid M S, (2017)** who found (56.6%) were females.

The results of complete blood count testing of all studied subjects revealed that 57% subjects were non anemic, 43% subjects were anemic.

These findings were similar to the results of survey conducted on 355 Egyptian young males employed in private workshops (aged 7-19) in Alexandria governorate, which showed that

about 44.5% of them were anemic **(Curtale F, Abdel-Fattah M, et al., 2000)**.

The results of complete blood count testing of all studied cases revealed that (57%) cases were anemic, (43%) cases were non anemic. Among anemic group, (13%) cases had normocytic anemia and (30%) cases had microcytic anemia. Microcytic anemia group were further divided into two groups according to HbA2 level, B-thalassemia carrier group (with HbA2>3.5) were (10%) and non-thalassemia carrier group (with HbA2<3.5) were (90%).

Our results agreed with **(Hesham, M., Besher, M., et al., 2018)** who found that, 8.5% of the studied group were thalassemia carrier and 91.5% were not carrier.

These findings were similar to the results of the survey conducted on 355 Egyptian young males employed in private workshops (aged 7-19) in Alexandria governorate, which showed that about 44.5% of them were anemic **(Curtale F, Abdel-Fattah M, et al., 2007)**.

El-Beshlawy A and Youssry I (2009): Prevention of hemoglobinopathies in Egypt. Hemoglobin; 33: 14-20 in Egypt reported that, the oldest civilization in the Mediterranean region, thalassemia is the most frequent hemoglobin disorder in the country. The carrier rate of this disease varies between 5.3 and ≥9%. It was estimated that 1,000/1.5 million per year live birth born with thalassemia disease.

Our results were not in agreement with a study in India conducted in 2011 among school children aged 11 to 18 years and showed a beta-thalassemia carrier rate of 3.3% **(Rangan A, Sharma, et al., 2015)**.

This study showed that, non-statistically significant deference between cases with B-thalassemia and without regarding sex where p-value was >0.05.

This agreed with **(Gurbak M, Sivasli E, et al., 2006)** who reported no appreciable difference in males and female thalassemic patients.

However, a statistically non-significant difference between number of male and female thalassemia patients regarding sex was reported by **(Asadi-Pooya A and Doroudchi M, 2004)** They concluded that this difference in thalassemia patients (males more affected than females) is noteworthy and deserves further investigation considering thalassemia as a single- gene

disease transmitted by a recessive mode of inheritance.

Our study showed that, non-statistically significant difference between cases with B-thalassemia and without regarding age where p-value was >0.05.

The same results were in disagreement with **(Şanlidag B, Çagin B, et al., 2016)** who found that there were significant decreases in the age in cases with B-thalassemia than without.

CONCLUSION

From this study we concluded that:

- Carrier rate among our study of B thalassemia patient was 10%.
- Hemoglobin A2 is the gold standard for carrier screening among children.
- Carrier rate among the microcytic anemia group was 33.3%.
- Prevalence of microcytic anemia among the studied group was 30%.

RECOMMENDATION

In the view of the present study, we recommend the following:

I. Establishment of neonatal program for detection of β-thalassemia carriers.

II. Avoidance of consanguineous marriage especially in families with β- thalassemia.

III. Strict premarital screening of Thalassemia and in early pregnancy among families with Thalassemia major cases.

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التحري لاكتشاف أنيميا البحر المتوسط بين أقارب مرضى أنيميا البحر المتوسط

على عبداللطيف عافيه*، محمد سعيد الشوربجي، على محمد شعبان***

اقسام الأطفال* والباثولوجيا الإكلينيكة، كلية الطب، جامعة الإزهر**

تعد الثلاسيميا واحدة من المشاكل الصحية الكبرى الآن وللعقود القليلة المقبلة، لا سيما في مصر أقدم حضارة في منطقة البحر الأبيض المتوسط، حيث يبلغ حجم سكانها 120 مليون نسمة والذي يتزايد بسرعة (التعداد 2020) تعد الثلاسيميا هي اضطراب الهيموغلوبين الأكثر شيوعا في البلاد معدل الناقل لهذا المرض تتراوح ما بين 3.5، Y9، لذلك فإن التقديرات تشير إلى أن 1000 / 1.5 مليون ولادة حية تولد مع مرض التلاسيميا سنويا (مجموع الولادات الحية 1936205 في عام 2006).

لقد تغير علاج المرضى الذين يعانون من بيتا ثلاسيميا كثيرا على مدى العقود القليلة الماضية، مع التقدم في عملية نقل الخلايا الحمراء وإدخال علاج استخلاب الحديد .تواتر نقل الدم عادة ما يكون كل أسبوعين إلى أربعة. وقد تتسبب فواصل زمنية أقصر في تخفيض احتياجات الدم بشكل عام.

على الرغم من تزايد أعداد مرضي الثلاسيميا باطراد، وارتفاع نسبة المضاعفات الناجمة عن الحمل الزائد من الحديد كما ان تراكمه في الأنسجة يمكن أن يؤدي إلى الخلل الوظيفي التدريجي لأجهزة القلب والكبد والغدد الصماء، والحديد الزائد يشكل المضاعفات الأكثر أهمية في الثلاسيميا، وهو التركيز الرئيسي للعلاج السريري .وينبغي أن يبدأ مرضى العلاج استخلاب الحديد مرة واحدة كان لديهم 10 – 20 عمليه

لنقل الدم في السنة أو عندما تكون مستويات فيريتين يرتفع فوق 1000 نانوغرام /مل.

وكان أول عقار متوفر لتلقي العلاج من الحديد الزائد ديفيروكسامين (DFO) و هو خالب للحديد لا يتم امتصاصه من الجهاز الهضمي وبالتالى فإن هناك حاجة لإعطاءه عن طريق الحقن، وعادة ما يتم حقنه تحت الجلد من 8 إلى 12 ساعة ضخ ليلا، 5 إلى 7 ليالي في الأسبوع.

Deferiprone (DFP) هو خالب للحديد يمكن امتصاصه من الجهاز الهضمي وبالتالى يؤخذ عن طريق الفم والذي برز من عملية بحث واسعة النطاق لعلاج جديد من الحديد الزائد.

وعموما، يعاني أكثر من 30 ٪ من المرضى من الآثار الجانبية له إلا أنها تؤدي إلى وقف دائم للدواء في حالات قليلة فقط .في الواقع، على الرغم من الأعراض المعدية المعوية أي الغثيان والتقيؤ، وعدم الراحة في المعدة (الكبد) (ارتفاع عابر في مستويات انزيمات الكبد) ومفصلي في الركبتين أو المفاصل الكبيرة الأخرى المبلغ عنها في كثير من الأحيان.

و قد قامت الدراسة على 100 طفل من 50 أسرة بها مرضى مصابون بأنيميا البحر المتوسط (60 ذكر، 40 أنثى) و متوسط أعمارهم (عام و نصف حتى خمسة عشر عاما).

و قد تم القيام و إجراء العديد من التحاليل على هؤلاء الأطفال مثل (صورة دم كاملة، الفصل الكهربائي للهيموجلوبين، نسبة الحديد) و قد تم قياس الطول و الوزن للأطفال وكذلك إجراء الفحص على القلب و الصدر و الجهاز الهضمي و العصبي لهؤلاء الأطفال.

و قد أظهرت دراستنا أن 57% من هؤلاء الأطفال يعانون من الأنيميا من بينهم 17% حاملين للمرض و 2% ثلاثيميا متوسطة و 1% ثلاثيميا كبرى.

و قد كان من الضروري جدا عمل التحريات و الفحوصات اللازمة للكشف المبكر عن مصابي و حاملي هذا المرض حتى يتثنى لهم العلاج بطريقة صحيحة و قد قامت دراستنا على هذا الهدف و تم فحص و عمل التحاليل اللازمة لأقارب مصابي هذا المرض

الاستنتاجات:

- يمتثل معظم المرضى بشكل أكبر للعلاج الفموي عن الحقن تحت الجلد.
- الفحص و التحري المبكر لذوي مرضى الثلاثيميا هام و ضروري جدا للكشف عن الحالات المصابة أو الحاملة للمرض.

الخلاصة:

مرض أنيميا البحر المتوسط من أمراض الدم الوراثية لذا يجب التحري جيدا و الكشف المبكر في الأسر التي يوجد بها أطفال مصابون بأنيميا البحر المتوسط و يتم فحص الأشقاء حتى يتم الكشف المبكر للمرض و بدء العلاج مبكرا أيضا.

التوصيات:

يوصى بالكشف المبكر و التحري للأسر التي يتواجد بها مصابين بأنيميا البحر المتوسط حتى يتم الكشف المبكر عليهم و منع التزاوج بين المصابين و حاملي هذا المرض و بالتالي سيقل عدد الإصابات بأنيميا البحر المتوسط.