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Newly Diagnosed Cases of Major Hemoglobinopathies (2016-2021) in Duhok: How Effective is The Premarital Preventive Program?

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Abstract

Background and objectives: The hemoglobinopathy preventive program in Duhok has been implemented since 2008. We aimed to assess the effectiveness of the program through its ability to reduce the number of newly diagnosed cases.

Methods: In this retrospective descriptive study, we reviewed newly diagnosed major hemoglobinopathy patients in the period between Jan. 2016 and Dec. 2021 in Duhok, Iraq. Parents of patients were interviewed regarding premarital screening, counseling, and prenatal diagnosis. For those missed by former screening, further testing was performed.

Results: A total of 160 newly diagnosed major hemoglobinopathies over the study timeframe were recorded, with a modest decline of these cases from 35 in 2016 to 21 in 2021. Of the 160 cases, 150 were available for assessment. The parents of 50 patients (33.3%) did premarital screening: 43 were identified to be at risk, but seven were missed. The parents of 100 patients (66.7%), however, did not do premarital screening. The most frequent reasons for not seeking prenatal diagnosis being unaware of availability/being too expensive (57.5%), or for religious/cultural beliefs (35.0%).

Conclusions: The modest reduction in the numbers of newly diagnosed major hemoglobinopathies, should be viewed in context, but is below the ultimate aims of the program. There is a need to tackle the challenges posed by couples marrying despite risk, or before the program was initiated, as well as the availability, religious, and legal aspects of prenatal diagnosis and termination of affected pregnancies to ensure a more favorable outcome of the program.

Keywords: Hemoglobinopathies, Iraq, Premarital screening program

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Introduction

Beta thalassemia (β-thal) and sickle cell disease (SCD) are important health problems in the Eastern Mediterranean countries, including Iraq. In the Kurdistan region of Iraq, previous epidemiological studies revealed that the carrier rates for these two autosomal recessive disorders are 3.7-6.9% and 0.2-1.2%.[1] The problem is further aggravated by high rates of consanguineous marriages ranging from 24-27%.[2,3] The number of registered patients with symptomatic β-thalassemia and sickle cell disease in Kurdistan is more than 3000.[1] The impact on physical, social, emotional, and mental health of affected patients, and on the wellbeing of their families is huge, seriously reducing their quality of life, with grim prospects for their survival without bone marrow transplantation. Furthermore, these patients constituted an important health burden on the already overstretched health resources in the region, and a preventive program appeared necessary rather than optional.[4] Therefore, and following pilot studies, targeted and public educational programs, as well as molecular studies to determine the molecular basis of β-thalassemia, and after seeking the opinions of religious scholars regarding prenatal diagnosis and possible termination of affected pregnancies, the regional parliament passed a law making it mandatory to perform premarital screening for hemoglobinopathies, so the stage was set for the hemoglobinopathy preventive program to be initiated.[1] The preventive program in the region was based on premarital screening, identification of couples-at-risk (both partners are carriers of β-thalassemia and/or sickle cell trait), genetic counseling, and the offer of prenatal diagnosis (PND) in early pregnancy for the couples so identified, with understanding the termination of affected babies could be performed before the gestational age of 16 weeks.[5,6] The program was initiated in the three main provinces of Kurdistan since 2008, and the results of its first five years were promising in Duhok and Sulaimani provinces.[5,6] However, the effectiveness of any preventive program is judged by its ability to reduce the number of affected births in the targeted population. Accordingly, in the current study we aimed to review the number of newly diagnosed symptomatic β-thalassemia and sickle cell disease over a six-year period (2016-2021), and their parents' premarital screening records to assess the effectiveness of the program, and the challenges facing it.

Patients and methods:

In the period between 1st Jan 2016 and 31 December 2021, a total of 160 newly diagnosed patients with major hemoglobinopathies were registered at the main inherited blood disorders center in Duhok City, Iraq. In this retrospective descriptive study, the patients' records were reviewed and the records of their parents at the premarital center were sought. The parents were interviewed by phone, or in person if they visited the thalassemia center. The parents were asked about the date of their marriage, whether they had had a premarital screen done, and whether they were informed that they were couples at risk (both are carriers), and why did they not seek prenatal diagnosis. For those patients who were missed by premarital screening, repeat testing for the parents and their affected children was performed by full blood counts (CBC) (Swelab, Sweden), and high-performance liquid chromatography (HPLC) (BioRad-D10, USA). Molecular testing using Beta globin Strip-Assay (Vienna-Lab Diagnostics, Austria) was also performed in selected cases, as per manufacturer's instructions. The study was approved by the ethics committee at the Directorate of Health in Duhok, and Kurdistan Higher Council of Medical Specialties, and an informed verbal consent was obtained from all enrollees. Statistical

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analysis: The data were analyzed using (Microsoft Excel 2016 program).

Results:

One hundred and sixty patients were diagnosed and registered with major hemoglobinopathies in the timeframe of the study. They included β-thalassemia major/intermedia, and sickle cell disease. The distributions of these diagnoses over the six years reviewed are outlined in Figure (1). The latter figure shows that there was reduction in the number of newly diagnosed cases over the six-year time frame from 35 cases in 2016 to 21 in 2021, an overall reduction of 40%. Moreover, figure (1) shows that the reduction was 22.9% from 2016-2019, and a further reduction of 14.8%, and 8.7% over 2019-2020, and 2020-2021 respectively. Out of these newly diagnosed registered patients, the parents of 150 were reachable, and their data could be scrutinized. Of the latter 50 (33.3%) had their parents screened premaritally, while the parents of the remaining 100 (66.7%) did not have such screening.

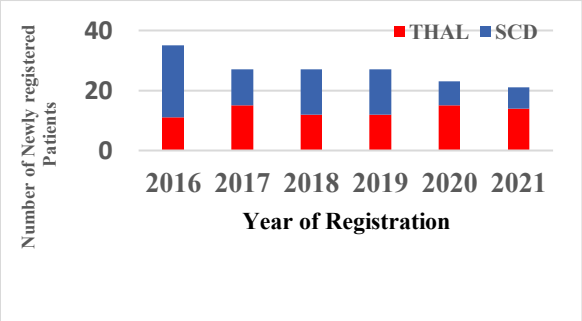

Figure (1): Newly diagnosed cases of major hemoglobinopathies annually (2016-2021) at the Duhok Inherited blood disorders center (Thal: Thalassemia major/Intermedia; SCD: Sickle cell disease).

Fifty of the parent-couples of affected children had premarital screening done, of whom 43 were identified to be at risk, while seven were missed. Of the former 43 couples, 39 (90.7%) confirmed that they had received proper genetic counseling, but only one did PND. The latter procedure was done in Turkey and revealed an unaffected fetus, but the baby was actually born affected with thalassemia major. The seven children whose parents at risk status were missed by premarital screening included: three with β-thalassemia major/Intermedia, three with sickle cell anemia (including a brother and a sister), and one with sickle/β-thalassemia. HPLC, CBC, and sickling test were redone at the time of the current study for all parents of these affected children and confirmed the carrier status of the parents, except for one male parent Table (1). The affected 5-year-old child (Patient I) of the latter parent is β-thalassemia major on the hyper-transfusion program and her β-genotype was IVS2.1 (G>A)/ γδβ thalassemia, while her father was molecularly characterized as γδβ thalassemia carrier Table (1). In one of the two other thalassemic families, one parent had borderline HbA2 Table (1). On the other hand, in the three couples who had sickle cell disease children, the slide sickling test of the male parent was reported negative at the time of premarital screening, so no further testing was performed for these couples then, and was reported by the premarital program as not-at-risk couples. A total of 100 patients (66.7%) did not have their parents premaritally screened. They included 11 whose parents were married after 2008 in areas where the screening program was not mandatory and moved later to the Duhok region. While 89 were married before the initiation of the program in 2008. Of the latter subgroup, 47 did not have any affected children, and the current baby was their first affected one, while 42 had previously had at least one affected child. There were 80 couples who were aware that they were at risk (38 identified by the premarital program and counseled + 42 non-screened couples who had at least one affected child), yet they did not choose to perform PND. The most

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frequent reason for not seeking PND were either because they were unaware of its availability or thought that it was too expensive (57.5%), while the second most frequent one was religious concerns or cultural belief in fate (35.0%) Table (2).

Table (1): The hematological and molecular (in selected cases) findings in the six parent-couples and their seven affected children that were missed by the screening program.

	Hb (gm/dl)	MCV (fL)	MCH (pg)	Hb A2 (%)	Hb F (%)	Molecular characterization Or HbS %	Parents married in
The patient (I)*	5.8	60.7	18.8	1.4	60	IVS2.1 (G>A)/ γδβ thalassemia	2017
Father of I	10.2	58.4	18.5	2.8	<0.8	γδβ thalassemia carrier	
Mother of I	11.2	59.2	18.9	4.1	<0.8	IVS2.1 (G>A) carrier	
Patient (II)*	7.9	65.8	22.0	2.3	63.0	IVSI.1 (G>A)/ IVSI.110 (G>A)	2019
Father of II	12.7	62.6	19.7	4.1	<0.8	NP	
Mother of II	9.7	67.2	21.1	4.6	<0.8	NP	
Patient (III)*	6.4	62.0	20.0	0.7	98.0	IVS1.130 (G>C) / Codon 8/9 (+G)	2008
Father of III	12.5	64.0	22.0	5.1	1.0	NP	
Mother of III	10.8	67.0	23.1	3.8	<0.8	NP	
Patient (IV)	5.0	86.4	26.2	1.6	23.2	Hb S: 65.1%	2017
Father of IV	13.6	86.0	28.0	3.1	<0.8	Hb S: 30%	
Mother of IV	11.5	80.0	26.5	3.2	<0.8	Hb S: 35%	
Patient (V)*	8.4	61.3	19.4	4.2	31.6	Hb S: 51.0%	2017
Father of V	14.0	82.0	27.2	3.0	<0.8	Hb S: 34.5%	
Mother of V	10.9	63	19.2	4.1	<0.8		
Patient (VI)*	8.9	79.4	25.4	2.2	14.3	Hb S: 78.1%	2017
Patient (VII)	9.6	72.9	23.4	2.7	22.4	Hb S: 59.5%	2017
Father of VI and VII	14.5	80.6	26.2	3.1	<0.8	Hb S: 35.3%	
Mother of VI and VII	11.0	74.4	23.7	2.3	<0.8	Hb S: 38.3%	

*Hematological findings at diagnosis; NP: not performed.

Table (2): Reasons given by 80 at-risk-couples for failure to uptake prenatal diagnostic test.

Reasoning behind failure to uptake prenatal diagnosis testing	Number (%)
We were not aware of the availability of prenatal diagnosis	31 (38.75)
We were aware of availability of prenatal diagnosis, but it is too expensive	15 (18.75)
Prenatal diagnosis is a dangerous procedure, or may damage the fetus	2 (2.5)
We do not trust the prenatal test	4 (5.0)
There is no need to do prenatal tests because we accept what God will give us	18 (22.5)
Even if we do the test, it is religiously unacceptable to terminate affected pregnancy	10 (12.5)

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Discussion:

The ultimate goal of any hemoglobinopathy prevention program is to have zero affected children born, or at least achieve a significant reduction of at least 65% of these births.[7] In the current study, we noted that there has been a drop in the number of newly diagnosed cases over the six years' timeframe. This drop, while encouraging, should be viewed with some caution, since in 2016 we had many internally displaced people due to the armed conflict in the surrounding regions registering their newly diagnosed hemoglobinopathy patients in Duhok, but as cessation of hostilities ensued by the end of 2017, those internally displaced people returned to their homes, and would have rather registered their affected babies in their local hemoglobinopathy centers. Furthermore, the effect of the COVID-19 epidemic in 2020 and 2021 may have led to delays in seeking medical advice and thus reduced the number of newly registered cases in these two years. Moreover, the opening of a satellite hemoglobinopathy center in Akre to the East of the province about nine years ago diverted patients from the main hemoglobinopathy center in Duhok City. Our results, however, are not as favorable as those reported by several preventive programs in the Middle East and the Mediterranean where remarkable reductions in the numbers of affected births with major hemoglobinopathies were reported.[7] In Sicily an 85% reduction was reported over 30 years, Similar reductions were also reported in Sardinia. [8,9] Likewise, results from Cypriot and Greek preventive programs yielded almost no affected births since the turn of the century.[7,9,10] Moreover, studies from Southern Iran revealed that β-thalassemia births decreased by 81%, and a 29-fold reduction was reported from Central Iran after about a decade of application, while a reduction of 90% was reported from Turkey.[7,11,12]One of the reasons behind our less favorable results is that 66.7% of parents of the affected children did not have premarital screening done, since they were either married before 2008 (89%) or because they were married after this year but in areas not covered by the program (11%). In an earlier study outlining the first five years of the premarital program in this same province, 77.9% of affected babies born had their parents married before the initiation of the program; while the respective figures reported from Central and Southeastern Iran in 2012-2013 was 51.4% and 78%.[6,11,13] This high proportion of unscreened parents should in our opinion trigger parallel screening programs in the population to address this gap in screening through antenatal screening in early pregnancy (< 12 weeks), or preconception screening. Although such parallel programs may prove costly, yet they are likely to be transient, since in 5-10 years the majority of the married population would have been covered by the mandatory premarital screen. The finding of six missed at-risk-couples (parents of seven affected children) is important, though it should be viewed in context. The premarital screens in these missed cases were performed in 2008, 2015, 2017, and 2019, when nearly 30,000 couples were screened. Furthermore, they contribute only 4.7% of affected newly registered patients. An earlier study from Iran reported screening test misses in 4.6% of their newly registered affected patients.[11] Furthermore, it is necessary to consider these misses in the original setting of the premarital screening program in the province, where the initial step was to screen the male partner by MCV, MCH, and slide sickling test, if these were normal, then no further testing for the female partner was required; On the other hand, if any were abnormal, then the female partner is tested and if both partners are abnormal, then further testing by HPLC was done. If both partners were confirmed as carriers, then the couples were labeled

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"couples-at-risk". Looking at the actual cases missed, three of the couples were parents of four patients with SCD and were missed because of a missed positive sickling slide test for the male partner triggering no further testing and thus were labeled as "not at risk" at the time. Of the three missed cases of thalassemia major/intermedia, one patient had a father with hypochromic microcytic indices but normal hemoglobin A2 and F, and this profile could be encountered in iron deficiency anemia, α-thalassemia, β-thalassemia with δ-mutations or in γδβ thalassemia. Except for iron deficiency, all the other possibilities require advanced molecular testing,[14,15,16] which was not available at the time. The father in this particular case turned out to be γδβ thalassemia carrier. Fortunately, δ-mutations and γδβ-thalassemia are rare disorders, though they constitute causes for missed identification of couples-at-risk.[16] Another cause of missed identification of couples at risk is borderline A2, which was documented in the female partner in one case in the current study. Borderline HbA2 or even normal A2 have been associated with β-thalassemia mutations in about 30% or even higher proportion of cases.[17,18] These observations stress the need to introduce molecular testing in selected couples with unexplained hematological findings or borderline A2 as part of the program.[19,20,21.] These missed cases led the premarital center to modify their standard operating procedures in 2018, by performing CBC and slide sickling tests from both partners from the start, and if any were abnormal, to do HPLC to both. Interestingly, out of the seven missed cases, the parents got married in six instances before the institution of this new policy. It is interesting to note that among the couples who were identified to be at risk and appropriately counseled, most parents chose not to perform PND, either because they did not know of its availability or its cost, others did not consider it for religious reasons or for their belief in fate. Similar reasons for declining PND were also cited by parents of newly affected cases from Iran.[11,13] While in developed countries, some couples opted to decline PND for ethical or religious restraints, misinformation, or because of improved life expectancy and quality in these countries.[8] In our country there is a need to increase awareness of the public or at least the couples-at-risk of the possible pathways to limit their chances of getting affected hemoglobinopathy children, whether through chorionic villus sampling, or non-invasive methods like next-generation sequencing cell-free fetal DNA from maternal blood as a cost-effective alternative procedure.[20] Earlier studies from the Kurdistan region of Iraq had found that about 90% of couples identified to be at risk, would proceed with their marriage plans regardless;[6,22] Furthermore, the observation of the current study that the large majority of couples at risk chose not to undertake PND, implies that the ultimate aim of significantly reducing the number of affected births is unattainable. The approach to tackle this issue needs to start with revisiting the religious and legal restrictions to termination of affected pregnancies, which should be followed by educational programs to stress the impact of hemoglobinopathies on the life quality of patients and their families and the importance of its prevention. If the religious and legal hurdles are overcome, then the health authorities need to prioritize offering subsided PND and termination of affected babies prior to 16 weeks' gestation, as an integral part of a preventive program.

Conclusion:

It appears that while there is an apparent modest reduction in the numbers of newly registered patients with major hemoglobinopathies, this reduction should be viewed in context and is below the ultimate aims of the preventive program. There is a need to tackle the challenges posed by

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couples marrying despite risk, or before the program was initiated, as well as the availability, religious, and legal aspects of PND and termination of affected pregnancies to ensure a more favorable outcome of the program.

Conflict of interest:

None to declare.

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