Journal of
Genetic Disorders and Therapy

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Research Article Open Access

Hemoglobinopathies Profile in Southern Morocco

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Received Date: March 30, 2022 **Accepted on:** May 06, 2022 **Published on:** May 08, 2022

Citation: Marzouki N, Rabi A, Quiddi W, Harkati I, Elouafi A, Sayagh S (2022) Hemoglobinopathies profile in Southern Morocco. J Gen Disor Thera 1: 1-10.

Abstract

Hemoglobinopathies (HGP) are among the most common hereditary diseases in Morocco. They constitute a real public health problem given their frequency and the difficulties of treating them. We studied here Two hundred patients with anemic syndrome or microcytosis. There is a qualitative and quantitative analysis by Capillarys 2 flex piercing electrophoresis and High-Performance Liquide chromatography. The Homozygous Beta-thalassemia, drepanocytosis, S/ beta-thalassemia and Hemoglobin C disease patients' blood were sent for genetic confirmation. Unlike the northern zone, the most frequent hemoglobinopathies, here, are beta-thalassemia (17%) followed by sickle cell disease (10.5%), then hemoglobin C (6.6%), minor alpha-thalassemia (1.2%) and finally, O Arab /beta-thalassemia (0.6%). We report that iron deficiency is very common in patients with a percentage of 14, 5%. It's the pathology number 2 next to beta - thalassemia. Using IBM SPSS, no difference detected between intragroup means values of Hb A2, Hb F and Hb variant. Equally, the same result found between age classes groups in all type of hemoglobinopathies ($p<0.0001$). In addition, we note Well correlation between HPLC and CE values in thalassemia and hemoglobinosis.

Keywords: Hemoglobinopathies, Thalassemia, Drepanocytosis, Iron Deficiency Hemoglobin C, Hb A2, Hb F, Anova test.

Introduction

Hemoglobinopathies recognized as a hereditary anomaly; transmitted according to the autosomal recessive mode and affect the hemoglobin protein (Hb) [1]. Because of their high frequency and potential seriousness, these conditions represent a major public health problem worldwide. According to data from the health organization, 7% of the world's population carries an abnormal globin gene and in some regions of the world up to 1% of newborns affected by a hemoglobin pathology [2]. These pathologies are especially widespread in tropical regions and extended to the majority of countries due to the different migratory flows observed these last decades [3]. In Morocco, the epidemiology of hemoglobinopathies remains unknown. The WHO estimates the rate carriers in Morocco at 6.5%. A published study on the prevalence of thalassemia in the northern region of Morocco hospital shows that the Garb is the most touched [4]. In south of Morocco, no hemoglobinopathy prevalence studied until now. Our objective is to identify and estimate rate of different hemoglobinopathies, participate to treatment management of these diseases and to create national medical register.

The recent study, reports hematologic laboratory experience of CHU Mohamed VI in Marrakesh/Morocco over 3 years, and its contribution to the management of HGP. We propose results exploration of hemoglobinopathies cases, to study their epidemiological characteristics and discuss their clinical and biological features.

Patients and Méthods

Patients

These are patients showed at least twice in consultation or hospitalization as well as their family members. After their informed consent, they are included in studied series. A data sheet completed for each patient during the analysis of his medical record. It provides his clinical criteria and biological tests results. They present anemic syndrome, abnormal blood Count, blood smear anomalies and/or hemolysis signs (high LDH, high bilirubin or a drop in haptoglobin levels ...). Fortuitous discovery of an abnormal Hb fraction observed when measuring "HbA1c" by HPLC and during a family investigation in-patient's relative.

Methods

This prospective study conducted within the hematology department of the university hospital center Med VI of Marrakech. During study period between January 2015 and December 2017, 200 HGP patients followed up by our team. Clinical data, Hemogram, Biochemical assessment of hemolysis, personal and family history collected. The distribution of these cases varies depending on the year; a maximum of cases is in 2016 with 59% of patients. HPLC and CE (capillary electrophoresis) are available for analysis of Hb. Using HPLC (D10 Bio-Rad (California, USA), 200 samples were analyzed. The Sebia Capillarys 2 Flex Piercing analyzer (France) used for 158 samples tests.

Hemogram

This is the first examination giving useful information to suspect a hemoglobin abnormality. The patient must not have transfusion at least for four months ago [5]. The hematological parameters measured electronically by a red blood cell counter giving the erythrocyte count, the hematocrit, the rate hemoglobin, erythrocyte indices (MCV, MCH, and MCHC). The automatic counter used in the Hematology Laboratory is the Sysmex XE 5000.

Blood smear

Blood smear reports any cells abnormality (anisocytosis, poikilocytosis…and/or inclusions presence).

Capillary Electrophoresis (CE)

CE was performed following the manufacturer's guidelines for the Sebia Capillarys 2 Flex piercing system using reagents provided in the Capillarys Hemoglobin (E) kit (Sebia, Norcross, GA). The instrument analyzes EDTA whole blood for hemoglobin variants. The lysed red cells electrophoresed in alkaline buffer (pH 9.4) allowing separation directed by pH and endosmosis. Detection of hemoglobin fractions using absorbance at 415 nm. CE not require daily calibration, but normal Hb A2 control analyzed daily through each capillary before additional quality control if required (as AFSC, AF or normal/ abnormal Hb A2 controls) and in the end of runs. By this way, we ensure proper charge and function of the capillaries. Results recorded as an electrophoregraph and chromatograph which are then analyzed [6] [7] [8]. The electrophoretic profiles obtained allow qualitative and quantitative analysis of different hemoglobin found. Therefore, it is possible to determine the percentages of each hemoglobin fraction.

HPLC

HPLC analysis was performed using dual program (A2/F) by D10 (Bio-Rad, Marne la coquette, France), which sep-

arates hemoglobin fractions by cation exchange chromatography using his alkaline gradient. HbA2 and Hb F single point calibrators performed daily to adjust and ensure proper retention times and to establish calibration parameters for accurate quantification. Low and high controls evaluated at the front and the end of each run. Hb A1C calculated simultaneously by D10 A2/F program. Hb A1C>6% increase Hb F level (Hb F>1%). care should be taken in diagnosing diabetic patients.

Statistical Analysis

IBM SPSS used to look for means values of age, sex number, different hemoglobin variants, Hb A2 and F. Anova test evaluate intra and inter groups correlation: between percentage of hemoglobin (normal and pathological) and ages classes groups.

Ethics

All patients signed agreement and consent before analysis with respect for anonymity

Result

Age of patients

The patient's age at diagnosis time varied between 4 months and 67 years, with an average of 24.5 years (standard deviation: 18.8 years). In our series, patients are divided into 41.1% of men and 58.9% are women. There is a female predominance with a sex ratio M/F of 0.7 (Table.1).

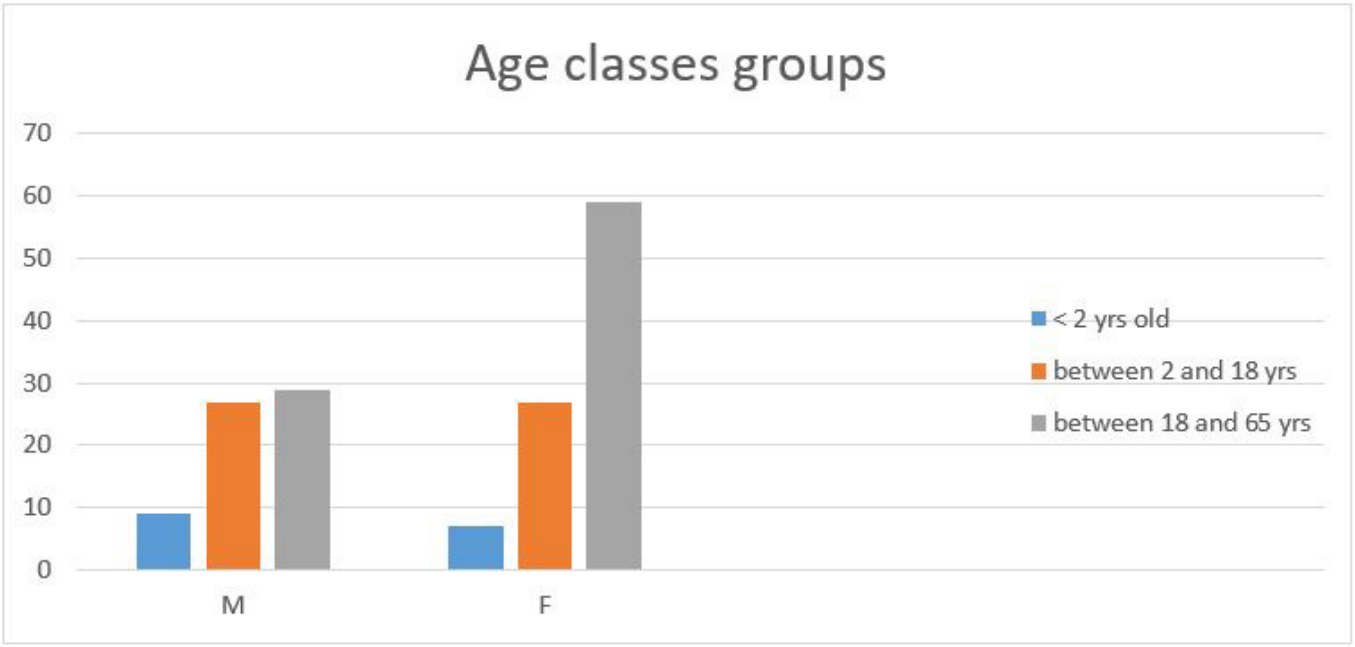

Figure 1: Classes Age in Southern Moroccan Hemoglobinopathies Patients.

Geographical origin of patients

The origin of the patients is variable: Most patients are from Marrakech (75%). Other patients are from Zagora, Tinghir, Kelaa, chichaoua, ouarzazate, all from south of Morocco. Only one from Guinee.

Blood count

Hemoglobin is lower (Hb <9 g/dl) in homozygous (B/B or S/S) and double heterozygous forms (S/B). Nevertheless, it is normal or moderately low in heterozygous Patients (Table.1). Severe anemia observed in 27% of HGP patients.

Parameters	Values
Hemoglobin: Hb <9 g/dl (27%) 9 g/dl <Hb <11 g/dl (56%) Hb > 11 g/dl (17%)	2,3 - 13,4 g/dl
MCV	44 - 115 μ^3,
MCHC	15 - 32,9
RBC	3000 - 6000/mm^3
platelets	54000/mm^3 - 315000/mm^3
Reticulocytes	15500 - 945000 g/l

Table 1: Variable parameters in blood count of hemoglobinopathies patients

Patient History:

About thirty-nine patients (25%) have a history of consanguinity. Therefore, consanguineous marriages contributes to increasing recessive HGP patient's number. Anemic syndrome and microcytosis are the most common reason for consultation (fig.2). The presence of frontal bumps, hypertelorism and enlargement of the malar bones in 1,2% of homozygous beta -thalassemia patients which are not treated earlier. A family history of HGP found in 16, 5% of cases. Family death story following HGP observed in 1, 2% of patients. Multiple transfusions showed in 7% of homozygous (BB, SS and some CC) or double heterozygous patients (S/B). In our study, age at onset of clinical signs and the first consultation varied between one and 36 months, with an average delay of 10 months (in homozygous B/B, SS or S/B).

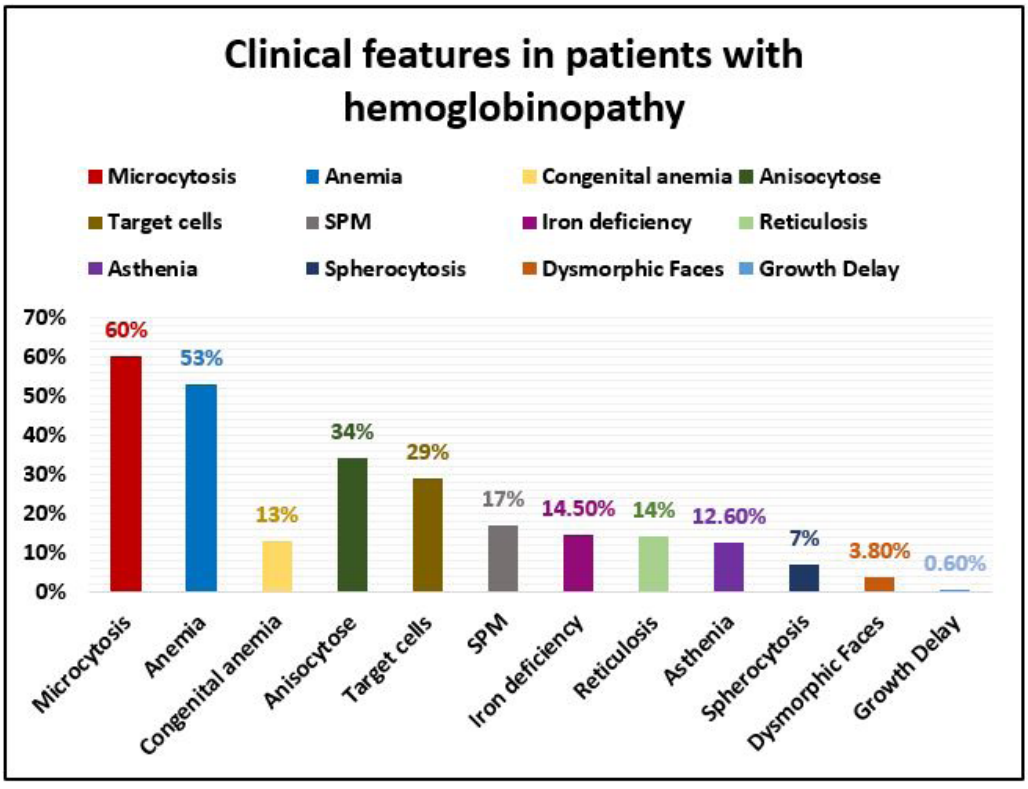

Figure. 2: Clinical features in patients with hemoglobinopathy.

ANOVA 1 factor inferior HBA2 and superior HBA2 with PATHOLOGY

Statistical analysis

Using IBM SPSS, no difference detected between intra-group means values of Hb A2, Hb F and Hb variant and inter groups (age classes groups in all type of hemoglobinopathies ($p<0.0001$). Well correlation noted between HPLC and CE values in thalassemia and hemoglobinosis (Table 2).

		Sum of squares	ddl	Mean of squares	F	Signification
HB_A2 Low limit	Intergroupes	1532,832	25	61,313	145,761	0,000
	Intra-groupes	55,525	132	0,421		
	Total	1588,357	157			
HB_A2 High limit	Intergroupes	1502,218	25	60,089	138,617	0,000
	Intra-groupes	57,220	132	0,433		
	Total	1559,438	157			

Table.2: ANOVA TEST of HbA2 values in pathological patients.

Hemoglobinopathy profile

It performed in all patients at least twice. Patients tested for hemoglobinopathy by capillarys 2 flex piercing and HPLC in Southern Morocco and show 59% patients carried or homozygous of hemoglobin defect. Beta –thalassemia is the most frequent form of HGP with 17% (table 3). 6% of patients have severe HGP form (HMZ beta- Thalassemia, SS or S/ beta-thalassemia) (Figure 3). Screening was done for siblings and parents of 18 patients (11,4% of cases). it Detects asymptomatic carrier parents of HGP in tested patients. The siblings are normal or heterozygous for thalassemia or hb variant.

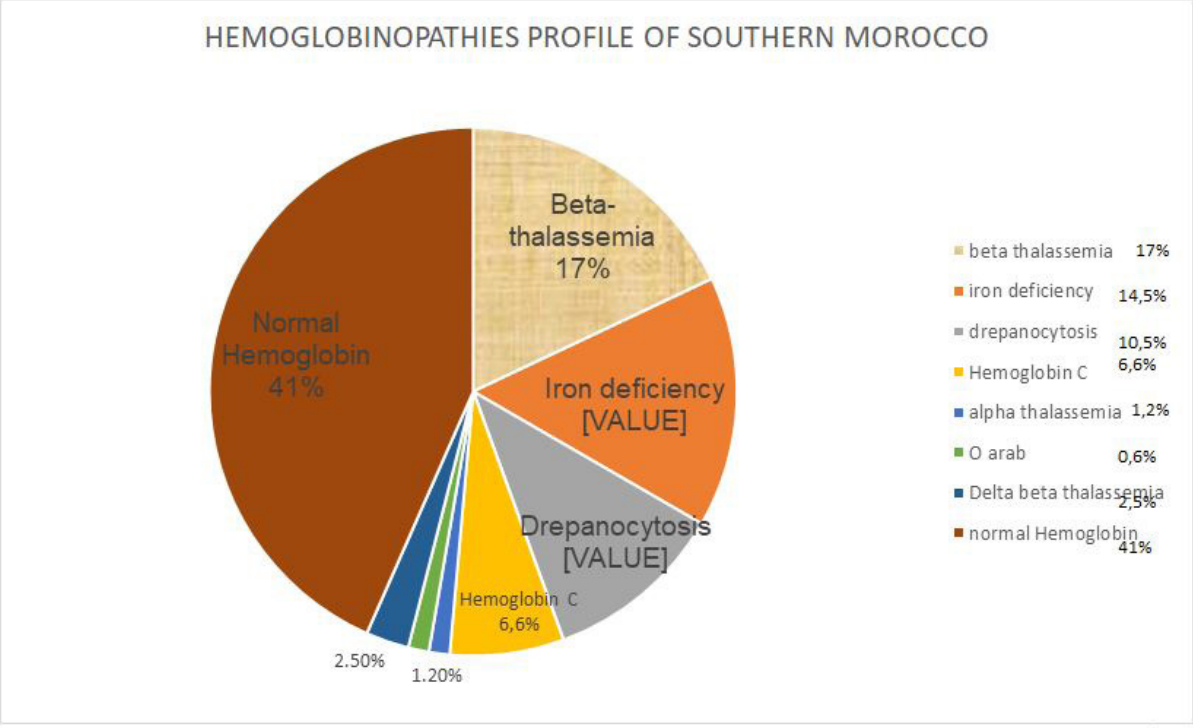

Figure. 3: Hemoglobinopathies profile in southern Morocco (this study).

DISEASE TYPE	Hb Anomalies	Percentage	Total
Beta- thalassemia (BT)	HTZ BT	14%	**17%**
	HMZ BT	3%	
Drepanocytosis (S)	A /S	7,5%	**10,5%**
	SS OU SB	3%	
Hemoglobin C	CC	2%	**6,6%**
	CA	4%	
	C Beta-thalassemia	0.6%	
Alpha-thalassemia	Alpha	1,2%	**1,2%**
Iron deficiency	Carence	14,5%	**14,5%**
Elevated Hb F	HbF <5% (nl Hemogram)	4,4%	**4,4%**
Delta-BT	Hb F>5% (Hb A2 normal or low)	2,5%	**2,5%**
Hb O Arabe	HTZ O Arabe Hb	0,6%	**1,2%**
	O Arabe/ BT	0,6%	

Table 3: Hemoglobinopathies profile in southern Morocco (this study).

Hb A2 and F Values Means

In patients having normal hemoglobin profile (normal alpha and beta globin gene), Hb A2 level is between [2,5%, 3,2%], while Hb F level is moderate (< 5%) (table 4).

The Homozygous BT have a normal or high Hb A2 (<7,2%) but, dominated Hb F. Heterozygous Beta- thalassemia patients have a high Hb A2(> 4%) and Hb F<3,7% (table 4). Normal or high Hb A2 detected in homozygous Drepanocytosis, but, an elevated Hb F was observed. Minor Alpha thalassemia patients show a lower Hb A2 level and normal Hb F. Delta beta-thalassemia cases present a normal hemoglobin A2 percentage but, elevated Hb F. They have an intermediate BT phenotype with anemia, microcytosis, asthenia and SPM.

Homozygous Hb C disease show normal Hb A2 and Hb F percentage. Blood smear show micro spherocytosis, Microcytosis, target cells, schizocytosis, jolly body and in severe form anemia, reticulocytosis, anisocytosis, thrombopenea and lymphopenea. C/Beta thalassemia show high Hb A2 level but it's normal in C/A patients (Table.4).

Hb Type	Type	HB_A2	HB_A2Bis	HB_F	HB_FBis
AA	NORMAL	2,6	3,2	1,6	1,9
HTZ Beta- Thalassemia	A / BT	4,3	7,2	0,0	3,7
	B/B	3,1	7,3	25,9	97,9
Drepanocytosis	S/S	2,2	6,2	6,8	21,3
	S /B	0,3	3,3	11,2	14,1
	A/S	2,8	4,4	0,0	2,9
Hemoglobin C	AC	2,8	3,3	0,2	0,4
	C/B	4,3	4,8	0,8	1,0
	CC	0,0	3,8	0,0	0,6
Delta beta thal	Delta BT	2,0	2,8	5,5	9,2
00%<Hb F<5%	Elevated Hb F	2,8	2,9	1,6	2,3
Alpha thalassemia	Minor alpha thalassemia	1,7	2,5	,0	0,0
O Arabe Hb	O arabe /BT	6,0	6,4	9,3	10,3
	Htz O Arabe	39,4	40,0	,0	,0

Table. 4: Hb A2 and F Values Means in Different Hemoglobinopathies Type in Our Study.

Discussion

The Epidemiological Level

In our series, the patients are divided into 41,1% Male and 58,9% females with a sex ratio M/F= 0.7, this female predominance was found at CHU Hassan II of Fez and in Italy with an M/F sex ratio of 0.6 and 0.9, respectively [9] [10]. However, male predominance found in CHU Ibn Sina in Rabat and CHU Farhat -hachet of Sousse in Tunisia, with a sex ratio 1.4 and 1.36, respectively [11] [12]. We find the same results in Tunisia and Algeria with a sex ratio 1.9 and 2.1, respectively [13] [14]. The female predominance cannot be explained by relationship between sex and disease since the transmission of this condition is autosomal recessive that it affects both sexes equally. Fifty six percent of patients had age superior to 18 yrs old. Age between 2 yrs old and 18 yrs old is in 34%. Less than 2 yrs old showed in 10% of patients (Figure.1).

In our series, 25% of cases have a consanguinity history. Therefore, our society has changed. It is beginning to accept marriages outside the family and even with strangers, especially, in south of Morocco. Furthermore, 52.5% of patients have a consanguinity history in University Hospital Hassan II of Fez (northern Morocco) [15]. Comparing to other countries in north of Africa, higher frequency of consanguinity observed: 68% in El-Owed region of Algeria [17], 65.6% in university hospital Hédi Chaker in Tunisia [12] and 35.5% in CHU Khelil Amarane in Algeria [13].

In our study, the age at onset of clinical signs and the first consultation varied between 4 months and 36 months (average of 20 months). 29.6% of patients consulted after 6 months due to low socioeconomic level. Therefore, this very late diagnosis lead to complication or death of homozygous form and explain predominance of heterozygous forms (14%, generally healthy patients).

Personal history in HMZ BT describe asthenia, congenital anemia, SPM, HSPM, poly transfusion per 20 days to one-month, repetitive infection, fever, icterus (hb<5), consanguinity first degree, dysmorphic faces, retroperitoneal lesion (tuberculosis or lymphoma), multi lithiasis gallbladder and/ or leishmaniosis. Splenectomy markedly improved their condition and reduced the level of Hb F. HMZ Drepanocytosis present congenital anemia, asthenia, Vasculopathy, Epistaxis, frequent transfusion, Growth delay and dysmorphic face in patients treated late.

Circumstances of discoveries

The revealing signs of beta-thalassemia in the present study dominated by: Anemic syndrome (88%), abdominal distension (1,5%), and abnormal blood count in 13.6% of patients which correlate with other studies [23, 24], excepting, in Tunisia [22] (who studied major thalassemia).

In our study, 66% of the HGP cases had an anemic syndrome, as described at the literature [23] [24] (Fig.1). SMG noted in all homozygous beta thalassemia patients and in 17% of HGP cases, HSMG is present in 11.5% of patients, which unlike literature result [13, 14, 15, and 16]. This is due to the predominance of heterozygous forms in our series.

Dysmorphic faces are more marked in severe forms with patients treated late and in those who benefit from an irregular transfusion program, while it is more discreet in patients treated earlier. In our cases, dysmorphic face is quite present (3,8%). Stunted growth showed in 0,6% of patients. It is a result of anemia, low levels of IGF 1 hormones and IGFB-3. But, also by erythroid lines expansion [25].

Biological criteria

Heterozygous carriers of βT typically present a rate low mean corpuscular hemoglobin (MCH), a decreased MCV and an increase of HbA2 level (>4%) compared to (>5%) in other study (26). associated with a normal or slightly low Hb level. The smear blood shows less severe erythrocyte abnormalities than in homozygous subjects. The Hb level varied between 9 and 13.9 g/dl, with an average of 11,5 g/dl with rare schizocytes and microcytosis at smear. However, Homozygous β-thalassemia characterized by a very low Hb, MCV and MCHC level. Affected individuals present microcytosis, hypochromia, anisocytosis, poikilocytosis, schizocytosis, target cells, Jolly body, and circulating erythroblasts. The number of circulating erythroblasts (erythrocytes nuclei) correlated with the severity of anemia and increases after splenectomy. While, S/βT double heterozygosity, the Hb level is equally low and the smear showed the presence of (sickle cells + anisocytosis + target cells) in 12.3% of HGP patients. However, S/S patients present a more severe anemia necessitating frequent transfusion.

Hemoglobinopathy profile (our series)

Beta -thalassemia is the most frequent form of HGP in our cases studied. The same percentage observed in Northern Morocco. However, sickle cell disease affects less patients (10.5%) compared to northern patients with 80% of drepanocytosis patients. Delta beta –thalassemia, known as less frequent, observed in 2.5% and apparently our sufferers less tolerate this affection and most of them improved after splenectomy. Alpha thalassemia which is more frequent in north of our country (Laarech; 2,2%)), is less present in our patients (1.2%). Conversely, the variant C of hemoglobin is more important in southern Morocco with 6.6% comparing to the north.

We note that 4.4% of patients have an allele encoding persistent Hb F in adulthood (> 1 year) with a percentage (<5%) (Carrying two normal alpha and beta globin alleles). We note also that iron deficiency is very present in our series with a rate of 14.5% giving it a rank between that of BT first and SCD second.

In total, we have 59% of cases with hemoglobinopathies. The remaining patients have other anemic syndrome such as hereditary spherocytosis (1,2%), sideroblastic anemia (0,6%) or other hemolytic disease. According to the WHO, 17% affected by β-thalassemia [16]. We note the same percentage in our study. This rate declares BT as the first form of HGP in south of Morocco. The next one is drepanocytosis (10,5%). HTZ BT is more frequent (14%) in our series compared to other countries. This rate equally observed in Cyprus [2].

According to thalassemia distribution in Marrakech region, haouz, southern Morocco and the World Health Organization (WHO), Morocco is in 10th rank. Hemoglobinopathies correlated with a very low parasite density in infected patients and therefore protect against malaria [14]. This explains the location of Morocco in areas not endemic for malaria.

We note elevated Hb F in Moroccan beta thalassemia and drepanocytosis patients that can explain why some cases with lowest rate of Hb A or highest Hb S level, have moderate form of HGP. An increase in Hb F compensate lowest rate of Hb A in HMZ BT and inhibits the polymerization of sickle hemoglobin and the resulting pathophysiology. Hydroxyurea, an inducer of Hb F, has already approved for the treatment of patients with moderate and/or severe BT and SCD. These data suggest that the high Hb F levels in beta thalassemia syndromes and SCD result from increased erythropoietin levels. Possibly ineffective erythropoiesis gives a survival advantage to F cells.

Conclusion

Some difficulties encountered during HGP study: poor interrogatory and understanding parents' languages. Underestimated number of cases because some patients go to private laboratory and others are poor and do not even consult. These patients with very low socio-economic level have difficult follow-up.

This study declares that hemoglobinopathies are frequent in our country and threaten future newborns lives. Preventive measures must take place and avoid consanguineous marriages (or at less recommending premarital screening). This way can reduce HGP risks and death in coming years.

Acknowledgment

The authors appreciate family members who kindly contributed to this study.

Conflict of Interest

The authors declare no Conflict of interest.

Informed Consent

Consent forms read and signed by all patient's family

Author Contributions

NM, has designed and performed the study. NM, SS, WQ and AE have drafted the manuscript and did critical editing. IH and NM have assisted and supported in sample collection and subsequent analysis with statistics. WQ, SS and MN have carefully supervised this manuscript preparation and writing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article (and its supplementary files).

The Source of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. John Chapin, Patricia J. Giardina (2018) Thalassemia syndromes. Hematology 10: 546-570.

2. Joly P, Pondarre C, Cathérine B (2014) Les bêta-thalassémies: aspects moléculaires, épidémiologiques, diagnostiques et cliniques. Ann Biol Clin. 72: 639-668.

3. Bonello-Palot N, Cerino M, Joly P, Badens C (2016) Les thalassémies. Revue Francophone Des Laboratoires: 48.

4. Protocole national de diagnostic et de soins pour une maladie rare (2008) Syndromes thalassémiques majeurs et intermédiaires. Haute Autorité de Santé / Service des Maladies chroniques et dispositifs d'accompagnement des malades.

5. Robert GIROT (2012) Diagnostic biologique des maladies génétiques de l'hémoglobine. Journée de Biologie Clinique.

6. Belhadi K (2011) Etude des hémoglobinopathies dans la population de la région de Batna. Mémoire de magister en Biologie.

7. Lucile Jeanne (2010) Place de l'électrophorèse capillaire dans le diagnostic et le suivi des hémoglobinopathies. 21: 17-20.

8. Couque M, Montal Embert (2013) Diagnostic d'une hémoglobinopathie. Feuillets de Biologie 311.

9. Salah Mohamed EL Sayed, Ashraf AbouTaleb, Hany Salah Mahmoud, et al. (2014) Percutaneous Excretion of iron and ferritin (through Al-hijamah) as a novel treatment for iron overload in beta thalassemia major, hemochromatosis and sideroblastic anemia. Medical Hypotheses. 83: 238-246.

10. Pierre Aubry. Bernard-Alex Gaüzère (2014) Thalassémie Actualités. Medecine Tropical 5.

11. Romdhane H, Amara H, Abdelkefi S, Souyeh N, Chakroun T, Jarrey I (2014) Profil clinico-biologique et immunohématologique des patients atteints de beta thalassémie en Tunisie: à propos de 26 cas. Transfusion clinique et biologique.

12. Maaloula, O. Laaroussib, I. Jedidib, L. Sfaihia, S. Kmihaa, T. Kamouna, H. Alouloua, M. Hachicha (2017) Prise en charge thérapeutique des patients atteints de bêta-thalassémie majeure dans un service de pédiatrie du sud tunisien : à propos de 26 cas. Transfusion Clinique et Biologique.

13. Youna B, Hassina K (2017) Etude de la prévalence de la beta thalassémie dans la région de Bejaia. Mémoire de Fin de Cycle En vue de l'obtention du diplôme Master.

14. Conte R, Ruggieri L, Gambino A, Bartoloni F, Baiardi P, et al. (2016) The Italian Multiregional Thalassemia Registry: centers characteristics, services and patients' population. Hematology.

15. Lahlou S (2016) Profil épidemio-clinique, biologique, therapeutique et evolutif de la thalassemie chez l'enfant. Expérience de l'unité d'hémato-oncologie pédiatrique du CHU Hassan II de Fès. Mémoire de fin d'études.

16. Kawtar Tali (2015) La thalassémie menace 3.000 enfants marocains : Le dépistage précoce est de mise. http://aujourdhui.ma/societe/la-thalassemie-menace-3-000-enfants-marocains-le-depistage-precoceest-de-mise-118262.

17. BEDIR L (2006) Prévalence de la thalassémie dans la wilaya d'el oued. Mémoire de fin d'études. http://e-biblio.univ-mosta.dz › bitstream › handle.

18. Yacouba Issaka R (2015) La Bêta-thalassémie : Étude d'une cohorte de cas colligés au Laboratoire de Biochimie et de Toxicologie de l'Hôpital Militaire d'Instruction Mohamed V (HMIMV)- Rabat. Thèse de pharmacie.

19. Montalembert MD (1984) Syndromes thalassémiques.

20. Girot R, Montalembert MD (1995) Syndromes thalassémiques. In : Schaison G, Baruchel A, Leblanc T éd. Hématologie de l'enfant. Paris : Flammarion Médecine- Sciences. 109-117.

21. Cappellini, Cohen A, Porter J, Taher JA, Viprakasit V (2014) Recommandations pour la prise en charge des thalassémies dépendantes des transfusions (TDT). 3éme édition.

22. Romdhane H, Amara H, Abdelkefi S, Souyeh N, Chakroun T, Jarrey I (2014) Profil clinico-biologique et immunohématologique des patients atteints de beta thalassémie en Tunisie : à propos de 26 cas. Transfusion clinique et biologique.

23. Youna B, Hassina K (2017) Etude de la prévalence de la beta thalassémie dans la région de Bejaia" Mémoire de Fin de Cycle En vue de l'obtention du diplôme MASTER soutenu juin.

24. Yacouba Issaka R (2015) La Bêta-thalassémie : Étude d'une cohorte de cas colligés au Laboratoire de Biochimie et de Toxicologie de l'Hôpital Militaire d'Instruction Mohamed V (HMIMV)- Rabat. Thèse de pharmacie.

25. Laosombat V, Viprakasit V, Chotsampancharoen T, Wongchanchailert M, Khodchawan S, Chinchang W, Sattayasevana B (2009) Clinical features and molecular analysis in Thai patients with HbH disease. Ann Hematol 88: 1185-1192.

26. Borgna-Pignatti C and Galanello R (2004) Thalassemias and related disorders. Quantitative disorders of hemoglobin synthesis," in Wintrobes Clinical Hematology, J. P. Greer, J. Foerster, J. N. Lukens, G. M. Rodgers, F. Paraskevas, and B. Glader 1319-1365.