Incidence of Genetic Disorders of Haemoglobins in the Hospital Population of Bahrain

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ABSTRACT

In a retrospective study, blood samples of 56198 Bahraini nationals received at the Pathology Department in Salmaniya Medical Centre over the six-year period 1982-1987 were analysed. Of the total, 5503 were neonatal samples and the rest non-neonatal. Amongst the latter, 68.82% showed abnormal haemoglobin, 56.56% showed sickle cell trait, 10.44% showed sickle cell disease and 1.82% showed other forms of abnormal haemoglobins including rarer ones. Amongst the neonatal samples, abnormal haemoglobin were detected in 44.35%: 24.2% were α-thalassaemia cases, 18.10% were sickle cell traits, and 2.1% were sickle cell disease. The highly variable concentration of the abnormal haemoglobin in both groups was also studied and analysed. Such high incidence of abnormal haemoglobin gene necessitates a prospective detailed study of the problem in general population followed by genetic counselling.

Studies of incidence and distribution of genetic disorders of haemoglobins in different countries in the Middle East have been reported in the last few decades. The important and prevalent disorders in this part of the world are sickle cell trait and sickle cell anaemia, followed by β- and α-thalassaemias. Sickle cell haemoglobin has been the commonest of all the abnormal haemoglobins with molecular abnormality caused by the replacement of glutamic acid in the 6th N-terminal of β-chains with valine.[1,2] The homozygous abnormality of this disease, sickle cell disease, was first reported by Herrick[3] and the first case of sickle cell anaemia in the Middle East was reported in Egypt by Abbasy.[4] According to Lehman,[5] sickling gene was first originated in the Arabian peninsula. Cases and incidence studies of sickle cell anaemia and sickle cell trait have been reported in the Middle East by several workers.[4-11] Thalassaemia is also prevalent in the Middle East. β-thalassaemia described by Cooley and Lee in 1923 was reported in Mediterranean immigrants in the United States.[12] It has homozygous genetic anomaly of the reduction or total absence of production of β-globin chains. This is widely dispersed in the Middle East and well-recognised in Saudi Arabia.[13,14] Similarly α-thalassaemia, a disorder of defective production of α-globin chains has also multiple phenotypes and is prevalent in several parts of the Middle East.[11,15-19] Considering the magnitude of the problem in Bahrain, the amount of published data in this field here, is indeed very minimal and the only study is that of Mohammad et al[20] on 10372 cord-blood samples. The purpose of this study is to determine the incidence of haemoglobinopathies and thalassaemias in hospital population to highlight the seriousness of this problem in Bahrain so that a detailed prospective study can be carried out.

METHODS

During the period from January 1982 to December 1987 samples of 56198 Bahraini patients were screened for abnormal haemoglobins. These included cases referred from other wards at Salmaniya Medical Centre, out-patient clinics, health centres and private hospitals. Expatriates were excluded from our study and a great deal of care was employed to avoid duplication of data. Blood was collected in bottles containing ethylenediamine tetra-acetic acid disodium salt (Na_2 EDTA Salt) which was used a anticoagulant. The method of Itano and Pauling as modified by Sergeant was used for sickling test prior to haemoglobin electrophoresis.[21,22] Special haematological tests including Hb electrophoresis on cellulose acetate paper and when necessary on agar gel, foetal haemoglobin estimation and quantification of abnormal haemoglobin by densitometry were carried out.[23-27] The values were

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analysed and tabulated but no sex analysis was carried out as haemoglobinopathies and thalassaemias are not sex-linked disorders.

RESULTS

Of the total 56198 samples, there were 50695 non-neonatal and 5503 neonatal. Samples of patients one up to one year of age were grouped as neonatal and those above one year as non-neonatal. Such separation was necessary because the natural occurrence of higher amount of haemoglobin F and lower rate of production of β-chains up to one year of age, make β-chain-containing adult haemoglobin and haemoglobin S less prevalent in neonates. Haemoglobin F is in negligible and undetectable quantity above the age of one year in normal cases. Amongst the non-neonatal cases, those manifesting abnormal haemoglobin patterns formed a striking majority of 34893 cases or 68.82%, whereas, amongst the neonatal cases, they were 2441 cases or 44.35% (Table 1).

Table 1
Incidence of abnormal haemoglobin

Group	*No. of cases studied*	*No. of with cases abnormal Hb*	*%*
Non-neonatal	50695	34893	68.82
Neonatal	5503	2441	44.35
Total	56198	37334	66.43

Table 2
Incidence of haemoglobin amongst non-neonatal cases

Hb patterns	*No. of cases*	*%*
Hb A/A (normal pattern)	15802	31.18
Hb S/A (sickle cell trait)	28675	56.56
Hb S/F (sickle cell disease)	4437	8.75
Hb S/S (sickle cell disease)	857	1.69
Hb A/F/A_2 (β-thal. major)	82	0.16
Hb A/A_2 (β-thal. minor)	446	0.88
α-thal. (multiple patterns)	235	0.46
Rarer forms	161	0.32
Total	50695	100.00

In the non-neonatal samples, the sickle cell abnormalities constituted the largest group with 28675 cases (56.56%) having sickle cell trait and 5294 cases (10.44%) having sickle cell disease (Table 2). In the latter, the ratio of *Hb S/F : Hb S/S* was found to be 5.17:1 (4437:857). The incidence of thalassaemia gene was found to be comparatively much lower comprising 1.5% of the total: β-thalassaemia major constituted 0.16%, β-thalassaemia minor 0.88%, and α-thalassaemia 0.46%. Other rare haemoglobinopathies formed only 0.32% of the total.

Amongst the 5503 neonatal samples, the normal *Hb A/F* pattern was seen in 3062 cases (55.6%). Sickle cell trait was found to be not an uncommon abnormality in the neonates, comprising 18.1% of the total which was a much lower rate of incidence than in the non-neonatal samples. Sickle cell disease too was found with much lower incidence rate (2.1%). Samples with *Hb Barts* formed the majority, 24.2%, with or without double heterozygous combination with sickle cell gene (Table 3).

Table 3
Incidence of haemoglobin amongst neonatal cases

Hb patterns	*No. of cases*	*%*
Hb A/F (normal pattern)	3062	55.6
Hb A/S/F (sickle cell trait)	995	18.1
Hb S/F (sickle cell disease)	114	2.1
Hb A/F/Barts (α-thalassaemia)	863	15.7
Hb S/F/Barts (sickle cell disease with α-thalassaemia)	85	1.5
Hb A/S/F/Barts (sickle cell trait with α-thalassaemia)	384	7.0
Total	5503	100.0

α-thalassaemia patterns with *Hb H* and/or *Barts* in non-neonatal cases showed varying patterns. The commonest was *Hb A/H*. Combinations with sickle cell gene were much less common (Table 4).

Other rare haemoglobins constituted 0.32% of the total; these included *Hb D* and *Hb O* in homozygous and double heterozygous forms of which *Hb A/D* was found to be the commonest with 0.16% incidence (Table 5).

Table 4
Distribution of α-thalassaemia haemoglobin patterns in non-neonates(N=50695)

Hb patterns	*No. of cases*	*%*
Hb A/H	170	0.334
Hb A/S/H	16	0.034
Hb A/S/Barts	21	0.044
Hb A/H/Barts	28	0.054
Total	235	0.46

Table 5
Incidence of rarer forms of haemoglobinopathies in non-neonates (N=50695)

Hb patterns	*No. of cases*	*%*
Hb A/D	80	0.160
Hb A/O	34	0.070
Hb S/O	30	0.060
Hb A/F/O	3	0.006
Hb D/D	8	0.016
Hb O/O	4	0.008
Hb S/D/F	2	0.004
Total	161	0.32

On quantitative estimation of abnormal haemoglobins, surprisingly striking ranges were seen in different patterns. *Hb F* varied between 2 to 40% in sickle cell disease with *Hb S/F*. The range between 4.1 to 20% included the majority of cases (76.28%) (Table 6).

Table 6
Distribution of *Hb F* in sickle disease samples of *Hb S/F*

Percent range of Hb F levels	*No. of cases*	*%*
2.0 to 4.0	857	19.55
4.1 to 10.0	1990	45.39
10.1 to 20.0	1354	30.89
20.1 to 40.0	183	4.17
Total	4384*	100.00

*Out of 4437 cases, data of 53 cases were unavailable

In β-thalassaemia major *Hb F* level showed a very wide range, from 10 to 77.3% (Table 7). In β-thalassaemia minor, *Hb* A_2 varied between 3.7 to 13.5% (Table 8). Values of *Hb* A_2 of 3.6% and below were taken as normal.

Table 7
Distribution patterns of *Hb F* levels in β-thalassaemia major

Percent range of Hb F levels	*No. of cases*	*%*
10.0 to 30.0	12	14.7
30.1 to 50.0	23	28.0
50.1 to 77.3	47	57.3
Total	82	100.0

Table 8
Distribution pattern of *Hb A2* levels in β-thalassaemia minor

Percent range of Hb A_2 *levels*	*No. of cases*	*%*
3.7 to 5.0	32	7.17
5.1 to 7.0	206	46.19
7.1 to 10.0	187	41.93
10.1 to 13.5	21	4.71
Total	446	100.0

Hb Barts was the commonest abnormal haemoglobin seen in 1332 cases of which 1071 were available for quantitative densitometric analysis. *Hb Barts* in α-thalassaemias varied over a wide range, from 1 to 40% (Table 9).

Table 9
Distribution pattern of *Hb Barts* level in neonatal α-thalassaemia

Percent range of Hb Barts	*No. of cases*	*%*
1 to 5	301	28.10
5.1 to 10	603	56.30
10.1 to 15	110	10.27
15.1 to 20	28	2.62
20.1 to 25	12	1.12
25.1 to 40	17	1.59
Total	1071	100.00

Non-neonatal cases of α-thalassaemia also showed similar ranges of *Hb H*, from 1 to 38% (Table 10).

Table 10
Distribution pattern of *Hb H* levels in non-neonatal cases of α-thalassaemia

Percent range of Hb H levels	*No. of cases*	*%*
1.0 to 10.0	30	25.44
10.1 to 20.0	65	55.08
20.1 to 38.0	23	19.48
Total	118*	100.00

* Out of 135 cases, data of 17 were unavailable

DISCUSSION

Haemoglobinopathies and thalassaemias are both genetic abnormalities of the haemoglobin molecule; the former being the structural abnormality in the polypeptide sequence of the globin chain, and the latter being the absence or reduction of any one or more of the globin chains. The study confirms the high frequency of both these abnormalities in Bahrain. The most common genetic abnormality encountered is sickle cell gene having an overall incidence of 63.25% in our sample (53.48% sickle cell trait and 9.77% sickle cell disease). This incidence is remarkably high when compared to reports from Saudi Arabia in which the total sickle cell gene in different regions varies between 4.3 and 30.2%.[12] In those regions, the sickle cell trait varies between 1.6 and 23.9%, the sickle cell disease between 1.0 and 1.7%, and those with heterozygous combination with thalassaemia between 1.0 to 20.5%.

The high incidence in our study is possibly due to the fact that a good number of cases were referred from the health centres for Hb electrophoresis after getting positive results from sickling test. Another report from Saudi Arabia records an incidence of 14.3% for sickle cell trait in 648 children one to four years old.[28] A study of cord-blood samples in Bahrain, has revealed the incidence of sickle cell gene to be as high as 13.5% which included trait, disease and double heterozygous forms.[20] It is comforting to note that in our series *Hb S/F* cases were 5.17 times more than the *Hb S/S* cases. The favourable protective role played by *Hb F* in sickle cell disease is well-recognised by several workers.[10-12,28,29] The first report of a mild form of sickle cell disease associated with an unusually high level of *Hb F* of 15 to 25% came from Kuwait.[30] In our series, *Hb F* varied between 2 to 40% with severity of the disease being inversely proportional to the quantity of *Hb F*. In Qateef region of Saudi Arabia, association of *Hb F* at steady high level in sickle cell disease has been the rule rather than exception.[31] High levels of *Hb F* in sickle cell disease has also been observed in Iran and in India.[32,33] Heterozygous combination of sickle cell disease with α-thalassaemia, as has been reported in other parts of the Middle East, also modifies the course of the disease; however, such cases are very few in our series.[12,14,34]

The incidence of β-thalassaemia was found to be much lower (1.04%) than that of the sickling deformity. Of these, the majority of cases were β-thalassaemia minor (0.88%) and the rest were β-thalassaemia major (0.16%). A milder variant of β-thalassaemia of apparently homozygous form appears to be common in the Middle East.[34,35] *Hb F* in our series of β-thalassaemia major varied from 10.0 to 77.3% in comparison with other studies which showed a range of 2.6 to 70%.[36] *Hb* A_2 levels were generally lower than 3.9% in all of them and have not been statistically analysed. α-thalassaemia showed still lower incidence (0.46%) amongst the non-neonatal cases. When grouped with neonatal samples having *Hb Barts* the overall incidence could be expressed as 2.74%. The haemoglobin patterns vary widely in α-thalassaemia depending on the phenotype. Co-existence of α-thalassaemia with sickle cell gene, which has been found in number of cases amongst the neonates, contributes positively to the course of the disease. The ranges of *Hb Barts* and *Hb H* concentrations varied widely.

α-thalassaemia was found to be the major abnormality in neonates appearing either singly or in combination with the sickle cell gene. The presence of *Hb Barts* was found to be a useful marker for α-thalassaemia. In our study, 24.2% of neonates showed the presence of Barts was in conformity with cord-blood study in which incidence of *Hb Barts* was 24.3%,[20] while in new born Saudi babies the incidence was found to be as high as 65%.[31] Yet the detectable incidence of α-thalassaemia is reduced remarkably in later life probably because majority of the cases are heterozygous α-thalassaemia 2, which get masked by low undetectable levels of *Hb H*. Only α-thalassaemia 1 continues to manifest itself with 2 gene deletions and higher levels of *Hb H*. The rarest of the haemoglobinopathies were those of *Hb D* and *Hb O* which occurred in trait, homozygous or double heterozygous forms.

These findings caution us about the remarkably high prevalence of abnormal haemoglobin gene which could exist in the general population as exhibited in the hospital population of this large sample study. The treatment of these cases is an enormous task placing strain on the national resources. Many cases of hereditary haemolytic anaemias may remain undetected if the abnormal haemoglobin concentration is very low for which the recourse is DNA and/or globin chain analysis. To assess the real magnitude of the situation, a prospective study of the

problem in general population appears to be highly mandatory. This should be coupled with institutionalised genetic counselling which will be an effective measure in the prevention of the high prevalence of this gene.

CONCLUSION

The prevalence of abnormal haemoglobin gene is remarkably high in Bahrain as found in this large-sample hospital-based study. The incidence of its different varieties are discussed and compared with that in other studies in the region. A detailed prospective study of general population to assess the magnitude of the problem, and an effective genetic counselling programme to check its high prevalence are both recommended.

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