Incidence of haemoglobinopathies detected through neonatal screening in the United Arab Emirates

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حالات اعتلال هيموغلوبيني كَشَفَ عنها فحص الولدان في دولة الإمارات العربية المتحدة

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الخلاصة: في كانون الثاني/يناير 2002، تم الشروع في برنامج ارتيادي لفحص الوِلْدان (حديثي الولادة)، للكشف عن مرض الخلية المنجلية في دولة الإمارات العربية المتحدة، وذلك في ثلاث مناطق صحية في إمارة أبوظبي. وتوضح هذه الورقة وقوعات حالات الخلايا المنجلية وحالات أخرى من الاعتلال الهيموغلوبيني، وحالات من حَمَلة الاعتلال الهيموغلوبيني، على مدى اثني عشر شهراً، وذلك باستخدام الاستشراب chromatography السائل العالي الأداء كطريقة التحري الأوَّلية. وكانت نسبة وقوعات حالات الخلية المنجلية بين 22 200 طفل حديث الولادة هي 0.04٪ (0.07٪ من مواطني دولة الإمارات و0.02٪ لأشخاص من غير مواطني الدولة). علماً بأن نسبة وقوعات خَلَّة trait بالكريات المنجلية الإجمالية هي 1.1٪ (1.5٪ بين مواطني دولة الإمارات و0.8٪ بين الأشخاص من غير مواطني الدولة). ولذلك يوصي الباحثون بضرورة إجراء مَسْح شامل للكشف عن الهيموغلوبين المنجلي على مستوى الدولة ككل.

ABSTRACT In January 2002, a pilot programme of neonatal screening for sickle cell disease was launched in the United Arab Emirates (UAE) in 3 districts of Abu Dhabi emirate. This paper reports the incidence of sickle cell diseases, other haemoglobinopathies and haemoglobinopathy carriers over a 12-month period using high performance liquid chromatography as a primary screening method. The overall incidence of sickle cell disease among 22 200 screened neonates was 0.04% (0.07% for UAE citizens and 0.02% for non-UAE citizens). The incidence of sickle cell trait was 1.1% overall (1.5% for UAE citizens and 0.8% for non-UAE citizens). Universal neonatal screening for sickle cell haemoglobin at the national level should be considered.

Incidence des hémoglobinopathies détectées dans le cadre du dépistage néonatal aux Émirats arabes unis

RÉSUMÉ En janvier 2002, un programme pilote de dépistage néonatal de la drépanocytose a été lancé aux Émirats arabes unis dans trois districts de l'Émirat d'Abou Dhabi. Cet article présente l'incidence des drépanocytoses, d'autres hémoglobinopathies et des porteurs d'hémoglobinopathies sur une période de 12 mois, la chromatographie à haute performance ayant été utilisée comme méthode de dépistage primaire. L'incidence globale de la drépanocytose chez les 22 200 nouveau-nés examinés était de 0,04 % (0,07 % pour les citoyens des Émirats arabes unis et 0,02 % pour les non-citoyens des Émirats). L'incidence du trait drépanocytaire était de 1,1 % en général (1,5 % pour les citoyens des Émirats arabes unis et 0,8 % pour les non-citoyens des Émirats). Le dépistage de l'hémoglobine S chez tous les nouveau-nés au niveau national devrait être envisagé.

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Received: 10/04/03; accepted: 15/03/04

Introduction

For at least 20 years it has been known that children with sickle cell anaemia have an increased susceptibility to severe bacterial infection, particularly from *Streptococcus pneumoniae*. The risk of major infection with this organism is greater in the first 3 years of life and can occur as early as 4 months of age. This infection may be the first clinical manifestation of disease and carries a case fatality rate as high as 30% [*1*].

The demonstration in 1986 that prophylactic penicillin markedly reduces the incidence of pneumococcal sepsis provided a powerful incentive for the widespread implementation of neonatal screening for sickle cell disease. Subsequent experience demonstrated that neonatal screening, when linked to timely diagnostic testing, parental education and comprehensive care, markedly reduces morbidity and mortality from sickle cell disease in infancy and early childhood [*2*].

Sickle cell disease is an autosomal recessive genetic disorder characterized by the presence of sickle haemoglobin (HbS) in red blood cells. The clinical manifestations of sickle cell disease result from variable degrees of haemolysis and intermittent episodes of vascular occlusion that cause tissue ischaemia and acute and chronic organ dysfunction. Heterozygous individuals have sickle cell trait, a generally benign, asymptomatic genetic carrier state [*3*]. Genes for sickle cell disease are common in people of African, Mediterranean, Middle Eastern and Indian ancestry and people from the Caribbean and parts of Central and South America [*4*].

The primary purpose of screening is to identify infants with sickle cell disease. Screening also identifies infants with other haemoglobinopathies and haemoglobinopathy carriers. Detection of infants with haemoglobin traits by screening of newborns and testing of other family members, affords an opportunity to identify and counsel couples at risk for having future children with clinically significant disease. Previously undiagnosed family members with the trait or disease can also be identified [*5*].

In the United Arab Emirates (UAE), the national neonatal screening programme started by screening for phenylketonuria in January 1995. Screening for congenital hypothyroidism was introduced in January 1998. In January 2002, the Ministry of Health decided to launch a pilot study for neonatal screening of sickle cell disease before expanding it at the national level.

The aim of this pilot study was to determine the incidence of sickle cell diseases, other haemoglobinopathies and haemoglobinopathy carriers in 3 districts of Abu Dhabi emirate through a 12-month period of the sickle neonatal screening programme.

Methods

This pilot study was performed in Abu Dhabi, Al-Ain and Western Region medical districts from 1 January 2002 to 31 December 2002. Primary screening was carried out using high performance liquid chromatography (HPLC).

In UAE, a standard form for neonatal screening is issued to every baby born in hospital, where 99% of deliveries occur, and mothers are informed about the procedures and importance of neonatal screening. Newborn infants are brought to the designated maternal and child health centre on the fifth day for collection of blood samples by heel prick onto filter paper (S&S

903, Schleicher & Schuell, New Hampshire, USA).

In this pilot study, the same filter paper used for thyroid stimulating hormone and phenylalanine testing was used for testing for sickle cell disease. For each sample, an 1/8-inch diameter disc was punched out from the collection card and placed into a separate sample vial, 0.5 mL deionized water was added and after standing for 30 minutes at room temperature the disc was removed [*6*]. Sample vials were analysed in the Abu Dhabi laboratories using the Variant HPLC system (Bio-Rad Laboratories, California, USA) for detection of haemoglobin (Hb) types F, A, S, C, D and E.

Samples positive for haemoglobinopathies were referred to the Abu Dhabi central hospital for confirmation by HPLC and isoelectric methods. After appropriate education and genetic counselling for the family, the maternal and child health genetic specialist doctor in each district recommended confirmatory testing of the infant before the age of 2 months (for haemoglobinopathy diseases) and before the age of 4 months (for haemoglobinopathy carrier traits). Testing of parents and other family members for all haemoglobinopathies, including thalassaemia, was recommended in order to help establish the correct diagnosis in some infants [*7*].

All infants confirmed with sickle cell disease started prophylactic penicillin therapy by the age of 2 months and follow-up was arranged with the cooperation of a consultant medical haematologist.

Results

During the 12-month period of the pilot study, 22 200 newborn infants were screened out of 23 244 total live births, i.e. a total uptake of screening of 95.5% (Table 1). There were 9165 infants of UAE ancestry and 13 035 non-citizens.

A total of 342 newborns screened positive for haemoglobinopathies (Table 2). In Abu Dhabi medical district, out of 178 positive screening results 6 were sickle cell disease (FS), 1 had non-sickle haemoglobinopathy (FE) and 171 were haemoglobinopathy carriers (FAS, FAC, FAD or FAE). In Al-Ain medical district, 144 positive screenings were detected: 3 were sickle cell disease (FS), 3 had non-sickle haemoglobinopathy (FC or FD) and 138 were haemoglobinopathy carriers. In Western Region, there were no cases of sickle cell disease and 20 haemoglobinopathy carriers.

The data indicated that the incidence of sickle-cell disease was 0.04% for total

Table 1 **Percentage uptake of the neonatal screening programme for haemoglobinopathies by medical districts of Abu Dhabi emirate**

Variable	Abu Dhabi	Al-Ain	Western Region	Total
No. of live births	13 613	8 494	1 137	23 244
No. of neonates tested	12 830	8 354	1 016	22 200
% uptake	94.3	98.4	89.4	95.5

Table 2 **Haemoglobin screening results of neonates by medical districts of Abu Dhabi emirate**

Condition	Haemo-globin pattern	No. of neonates			
		Abu Dhabi	Al-Ain	Western Region	Total
Sickle-cell disease[a]	FS	6	3	0	9
Non-sickle haemoglobinopathy					
Homozygous HbC	FC	0	1	0	1
Homozygous HbD	FD	0	2	0	2
Homozygous HbE	FE	1	0	0	1
Haemoglobinopathy carrier					
Sickle-cell trait	FAS	132	94	14	240
HbC carrier	FAC	6	5	0	11
HbD carrier	FAD	32	39	5	76
HbE carrier	FAE	1	0	1	2
Total		178	144	20	342

Hb = haemoglobin.
[a]***Sickle-cell disease: included 5 cases confirmed as homozygous SS and 1 case confirmed as S/β-thalassaemia.***

Table 3 **Incidence of confirmed sickle-cell disease, non-sickle haemoglobinopathy and haemoglobinopathy trait carriers in Abu Dhabi emirate by nationality**

Condition	UAE citizen (*n* = 9165)		Non-UAE citizen (*n* = 13 035)		Total (*n* = 22 200)	
	No.	%	No.	%	No.	%
Sickle-cell disease[a]	6	0.07	3	0.02	9	0.04
Non-sickle haemoglobinopathy						
Homozygous HbC	0	0.00	1	< 0.01	1	< 0.01
Homozygous HbD	1	0.01	1	< 0.01	2	0.01
Homozygous HbE	0	0.00	1	< 0.01	1	< 0.01
Haemoglobinopathy carrier						
Sickle-cell trait	137	1.49	103	0.79	240	1.08
HbC carrier	3	0.03	8	0.06	11	0.05
HbD carrier	37	0.40	39	0.30	76	0.34
HbE carrier	0	0.00	2	0.02	2	0.01
Total	184	2.01	158	1.21	342	1.54

[a]***Sickle-cell disease: included 5 cases confirmed as homozygous SS and 1 case confirmed as S/β-thalassaemia.***
n ***= total number of neonates tested.***
UAE = United Arab Emirates.
Hb = haemoglobin.

screened neonates. The incidence by citizenship was 0.07% (1:1528 for UAE citizens and 0.02% for non-UAE citizens respectively (Table 3). It is noteworthy that 5 out of 6 sickle-cell disease cases for UAE citizens were confirmed as sickle-cell anaemia (homozygous HbS) with a incidence rate of 0.06% (1:1833) and only 1 case was confirmed as sickle/²-thalassaemia, while all 3 sickle-cell disease cases in non-UAE citizens were confirmed as sickle-cell anaemia (homozygous HbS). The incidence of sickle-cell traits were 1.08% overall (1:92) (1.49% for UAE citizens and 0.79% for non-UAE citizens respectively). For the non-sickle haemoglobinopathies, the incidence for UAE citizens were 0.40% for HbD trait and 0.03% for HbC trait (Table 3).

Our data indicated that no parents with previously undiagnosed haemoglobin disease were discovered and only 10 couples at risk for future children with a sickle-cell disease were identified by follow-up of newborns with haemoglobinopathy carrier traits: 4 were AS/AS, 4 were AS/²-thalassaemia trait and 2 AS/±-thalassaemia trait (Table 4).

No cases of sickle cell disease or sickle cell trait were recorded from hospital records among the neonates screening normal and there was no disagreement between confirmed and positive screened cases. Thus the confirmed neonatal screening results had an apparent sensitivity of 100% and a specificity > 99%.

Of the neonates screening positive for haemoglobin diseases, 57% (4 of 7 positive cases) had a positive family history and of those screening positive for haemoglobinopathy trait, 48% (85 of 177 traits) had positive consanguinity in the UAE-citizen group.

Table 4 **Results of follow-up of neonates with haemoglobinopathy carrier traits, showing parents at risk of future infants with haemoglobinopathies**

Screening result	No. of couples
AS / AS	4
AS / β-thalassaemia trait	4
AS / α-thalassaemia trait	2
AC / AC	2
AC / β-thalassaemia trait	2
AC / α-thalassaemia trait	2
AD / AD	4

AS = sickle-cell trait.
AC = haemoglobin C trait.
AD = haemoglobin D trait.

Discussion

The primary objective of screening newborn infants for haemoglobinopathies is the identification of sickle-cell disease before the onset of symptoms. Mortality from sickle-cell disease is greatest during the second 6 months of life and is due to infections. Thus, newborn screening allows prophylactic antibiotics to be started at 2 months to prevent such infections [*78*].

This pilot scheme for testing for sickle-cell disease in Abu Dhabi used the same heel-prick blood sample as for the existing national neonatal screening programme for phenylketonuria and congenital hypothyroidism. HPLC was used as the primary screening method because it has quantitative capabilities as well as higher sensitivity and specificity than isoelectric focusing or two-tier electrophoresis (cellulose acetate and citrate agar electrophoresis). In addition, variant HPLC testing is fully automated, allowing for hundreds of samples to be run daily and the programme can detect

HbF, HbA, HbS, HbC, HbD and HbE in a 2.5 minute run-time [*9*].

The haemoglobin pattern for normal newborn infants, FA, shows that the red cells of contain fetal (HbF) and adult (HbA) haemoglobins, with the haemoglobin with the highest concentration listed first. The haemoglobin pattern or phenotype is due to predominance of HbF at birth. Newborns with sickle-cell trait have an FAS phenotype, with more HbA than HbS. Infants with sickle-cell disease, sickle cell/²-thalassaemia and HbS/hereditary persistence of fetal haemoglobin (Hb-S/HPFH) each have an FS phenotype on screening at birth. Follow-up and confirmatory testing should be mandatory for all clinically significant results [*10*].

Our study achieved a total coverage of screening for Abu Dhabi emirate of 95.5%, which is comparable to the international coverage standard (99%) [*11*].

The figures for sickle-cell disease (0.07%) and sickle-cell trait (1.49%) for UAE citizens in our study are slightly lower than earlier studies done in UAE, which found an incidence of 1.9% for sickle-cell trait [*12*]. Saudi Arabia has an incidence of 2%–27% for sickle-cell trait and about 1.4% for sickle-cell anaemia with the highest rates in the Eastern Region and the lowest in the Central Region of the country [*13,14*]. Bahrain, on the other hand, has a rate of 11%–18% for sickle-cell trait, and an incidence of sickle-cell disease of 2.1% among screened newborns [*15*]. Oman is reported to have an incidence of 10% for sickle-cell trait [*16*] and about 0.4% for sickle-cell anaemia [*17*].

No false negative or false positive results were detected in the confirmation of the neonatal screening results in our study. These results are in accordance with reported studies in many countries using HPLC as a primary screening method [*9,18*].

As regards the consanguinity rate for citizens, there was no difference between the consanguinity rate among the positive haemoglobinopathy carrier screening in our study (48%) and the normal UAE population (51%) [*19*].

It is noteworthy that all infants diagnosed with sickle-cell disease started prophylactic penicillin therapy by the age of 2 months. This is an important, because the success of a newborn screening programme for sickle-cell disease is measured not only by the number of infants diagnosed correctly, but more important, by the timely fashion in which these children receive appropriate medical care.

No parents with previously undiagnosed haemoglobin disease were discovered and only 10 couples at risk for future children with a sickle-cell disease were identified by follow-up of newborns with carrier traits. So an infant with the trait provides a "genetic window" into a family that may be at-risk for having a child with sickle-cell disease.

Another objective of the haemoglobinopathy screening follow-up services is the education of families so that they will be more knowledgeable about haemoglobinopathy carrier traits and not confuse benign carrier status with disease [*20*].

Conclusions and recommendations

The results of this 1-year pilot study for newborn screening for sickle-cell haemoglobinopathies suggest that universal neonatal screening for sickle-cell haemoglobin should be considered at the national level, in addition to developing comprehensive health strategies such as genetic counselling services, comprehensive early care and premarital and prenatal diagnosis for haemoglobin disorders.

Acknowledgements

We would like to thank members of regional screening programme Dr Reem Zayed and Dr Shadya Hassan, all the participating laboratory staff, our colleague Mrs Aysha A. from the department of Maternal and Child Health for her assistance, and M.R. Nasser Al-Oudaly, laboratory manager of Central and Al Jazira Hospitals, Abu Dhabi, United Arab Emirates.

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