Chapter 1

General Introduction and Definition of Concepts

Definitions & General Pathology

Sickle cell disease (SCD) is a human clinical syndrome resulting from inheritance either in homozygous state or compound heterozygous state of a red blood cell (RBC) abnormality affecting the globin part of haemoglobin (Hb). The RBC abnormality results from a point mutation whereby in the amino acid sequence of the beta (ß) globin chain, valine replaces glutamic acid at sequence 6 of the chain [Fig.1.1].

MAJOR β-CHAIN CHANGES

A. QUALITATIVE: Amino acid sequence variants

TpI

		1	2	3	4	5	6	7	8
Normal	HbA:	Val	His	Leu	Thr	Pro	Glu	Glu	Lys
	HbS	Val	His	Leu	Thr	Pro	Val	Glu	Lys
Abnormal									
	HbC	Val	His	Leu	Thr	Pro	Lys	Glu	Lys

TpXIII

		121	122	123	124	125	126	127	128
Normal	HbA	Glu	Phe	Thr	Pro	Pro	Val	Gln	Ala
Abnormal	Hb^{D}_{Punjab}	Gln	Phe	Thr	Pro	Pro	Val	Gln	Ala
	HbO_{Arab}	Lys	Phe	Thr	Pro	Pro	Val	Gln	Ala

B. QUANTITATIVE: Suppression β-thalassaemias

a. Partial

b. Complete

C. QUANTITATIVE: Deletion

a. Partial

b. Complete

When this change occurs, the RBC membrane alters under stressful circumstances and ceases to function normally. When such RBC's are viewed microscopically they are seen to be abnormal in shape. This abnormality in shape varies and could resemble a cigar, a boomerang or a sickle [Fig.1.2].

The latter is the most consistent and typical shape from which the name sickle RBC or just sickle (S) cell is derived. The resultant Hb is denoted HbS. The gene thus inherited is called the HbS gene as opposed to the normal adult (A) Hb denoted HbA or Hbß^{A} . So also is the HbS Hbß^{S}. The homozygous or compound heterozygous states are therefore HbAA (ßAßA) for normal homozygote, HbAS (ß^{A}ß^{S}) for the heterozygous carrier, HbSS (ß^{S}ß^{S}) for the sick homozygote and HbSX (ß^{S}ß^{X}) for the sick compound heterozygote where X or ß^{X} denotes co-inheritance of another ß–globin abnormality such as HbC (ß^{C}), HbDPunjab (ß^{D}), HbOArab (ß^{OArab}), HbE (ß^{E}) or Hb-beta thalassaemia (ß^{thal}). With the exception of ßthal , all the others are a result of a point mutation like in ß^{S} . ßthal

is a result of either complete or partial deletion or suppression of the ß–globin gene, resulting in $ß^{O}$thal or $ß^{+}$thal. In the latter, there is limited production of HbA up to 30%. Professional definition of SCD is therefore "Sickle hæmoglobin related clinical syndromes in which untransfused normal HbA when present, is less than 30%."

Epidemiology: HbS initially occurred mainly in the African tropics and in particular in malaria endemic areas (MEA) of the same regions. The association with the presence of malaria has always been intriguing. This way its occurrence has tended to be oceano-lacustro-riverine. It is the most common hæmoglobinopathy in comparison to the other ß-globinopathies. Of the latter, HbC was confined to West Africa, mainly in Ghana, ß-thal mainly in the mediterranean region and West-Central Africa and Asia, HbD^{Punjab} in India, and HbE in the far east. Through slave trade and later through increase in international communucation, these ß-globinopathies and some alpha–globinopathies reached the Americas and Europe [Fig (1.3)].

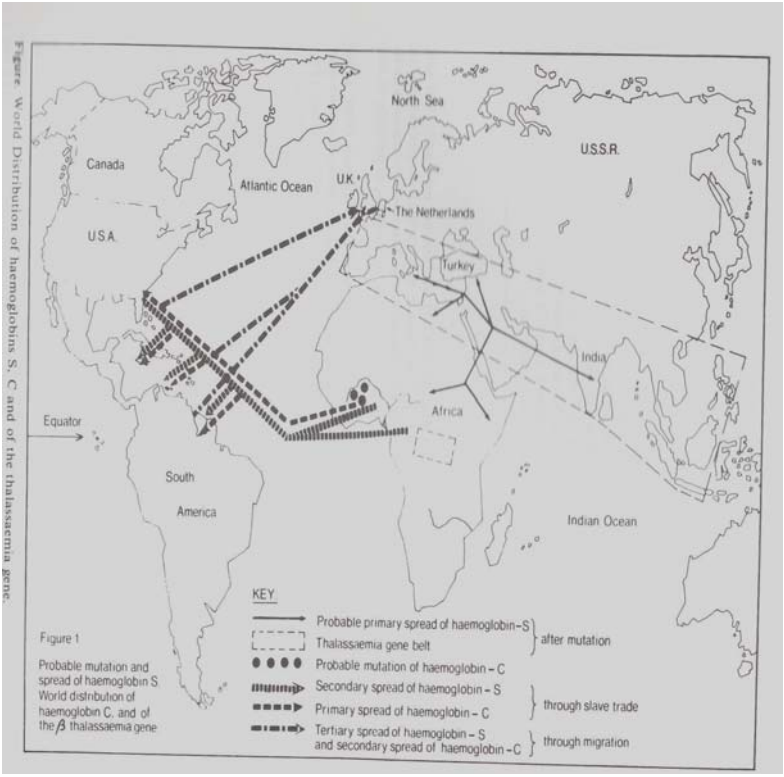


Fig. 1.3 World Distribution of Sickle Cell Gene and Other Related Haemoglobinopathies

HbS ranges from 1% in South Africa to 40% in central India and 45% around the "mountains of the moon" in Western Uganda. The next highest rates of occurence are around Lake Victoria in Kenya, Uganda and Tanzania and the east coast of Kenya. In the great lakes' countries of Rwanda and Burundi, sickle cell trait is around 3 %. Its highest rate in the Bamba of the Ruwenzori mountains at up to 45 % is rather curious and needs further confirmation as has been done on the Kambe of Kenya. HbS rates 8% in Afro-Americans in North America.

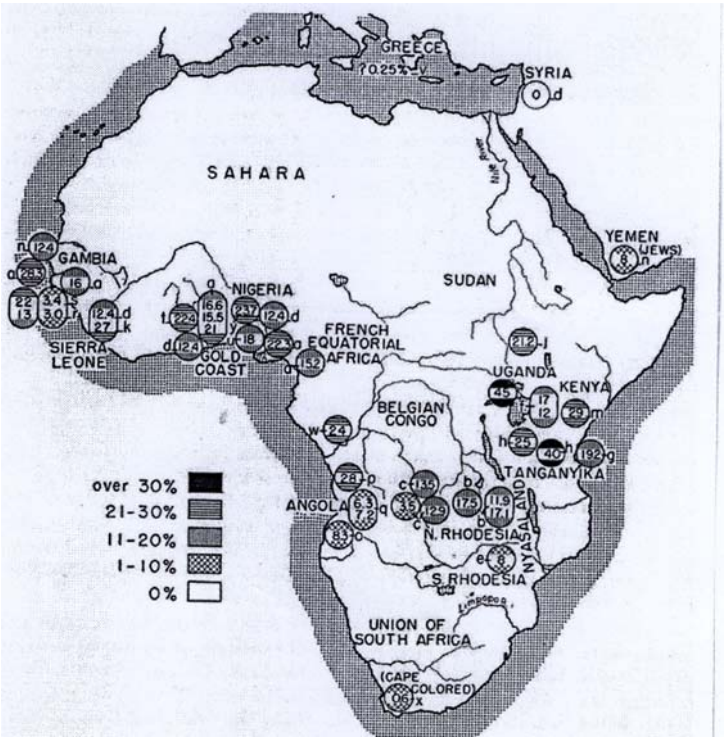
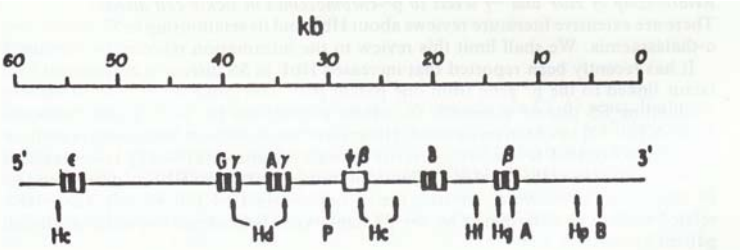


Fig. 1.4 Continental Distribution Of Sickle Haemoglobin in Africa (Adapted by permission from "The Anthropologist", 1959)

Clinical Heterogeneity

Clinically, HbSS disease, also known as sickle cell anæmia (SCA) is globally the most common type of SCD. However, in East Africa and the Great Lakes Region (GLR) it is the predominant form of the disease. This is because the $ß^X$ variants are either non-existent or very rare in East Africa so compound heterozygous forms with HbS do not occur. Phenotypically, HbSS ($Hbß^Sß^s$) disease is clinically more severe than the $Hbß^Sß^X$. Even within the HbSS genotype groups, there are clinical variations because of HbS differences at molecular level. These differences are determined by various haplotypes known as $ß^S$–haplotypes

[Fig.1.5].



Hc = Hinc II; Hd = Hind III; P = Pvu II; Hf = HinfI; Hg = HgiAI; A = Ava II; Hp = Hpa I; B = BamHI restriction enzymes.

Figure 4. The human β-globin cluster. Arrows indicate restriction enzymes and polymorphic sites.

The above ß-globin cluster looks rather complex and a somewhat simpler form is shown below.

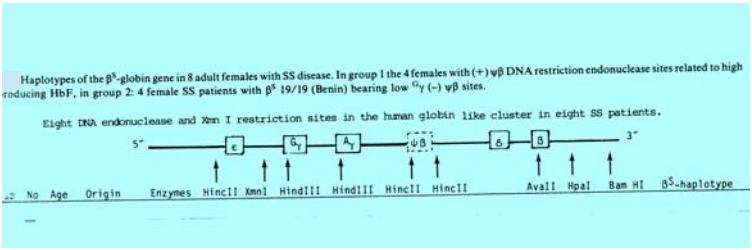
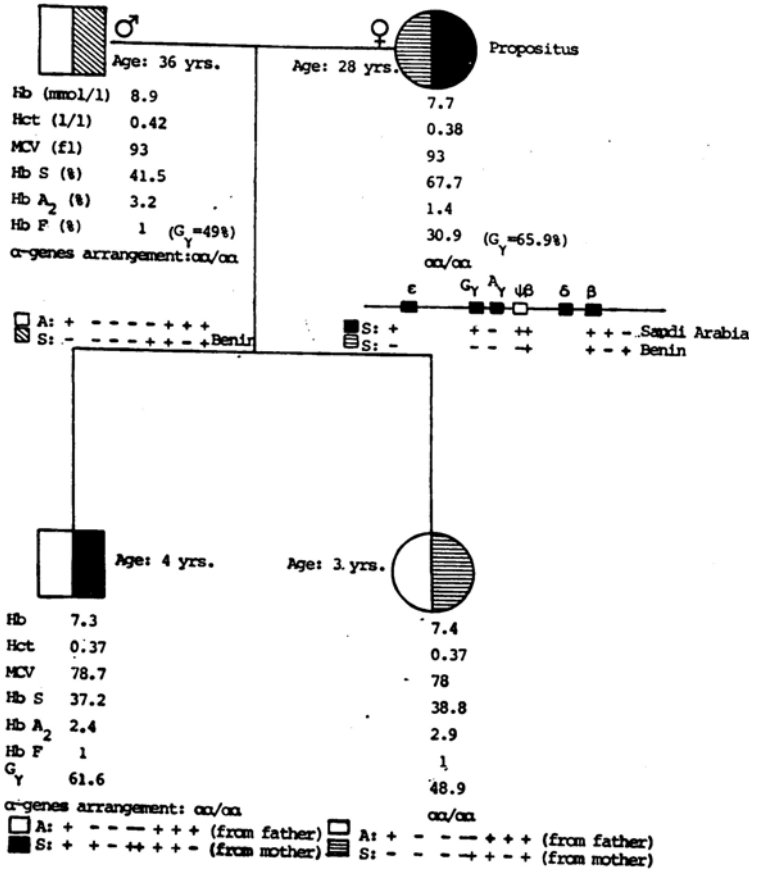


Fig 1.6

Both of the above are adapted from the doctorate work by the author.

The two Ses in one homozygote could be the same by alkaline electrophoretic testing but different by molecular hæmatologic methods. There are at least eight different ß^S-haplotypes. Of these the "Bantu" haplotype found in the Central African Republic (CAR) is clinically the worst type. This is the same ß^S-haplotype found in Kenya and is also known internationally as the "Kenya haplotype". Sickle cell anæmia in Kenya and the rest of GLR is therefore the worst type resulting in shortened life expectancy and clinical complications. The ß^S-haplotype could determine the clinical severity of SCD. This was the core of the author's doctorate work in the Netherlands as exemplified by one of the cases shown on the diagramme, a white woman from Turkey with HbSS disease who was compound heterozygous for two different ßS-haplotypes: the Benin and the Arabo-Indian haplotypes. [Fig. 1.7]



Her son inherited her Arabo-Indian HbS and the girl inherited the Benin ß^S-haplotype from the father. Both children were potentially at risk for SCD but escaped with only being carriers. This patient was discovered by chance as she reported for her second delivery. She rarely had clinical symptoms. Her case aroused curiosity by the author regarding the nature of sickle cell disease in the Netherlands.

A comparable case in Kenya who was much older than this white patient equally attracted interest for further studies in SCD in Kenya. It had in the meantime been established that the sickle cell gene at both coasts of Kenya were haplotypically identical to the one of the Central African Republic. There were, however, no data as to the nearest magnitude of the disease in Kenya where it had earlier been reported that SCD was a children's disease. There had equally been reports that Kenya had the third highest rate of sickle cell trait in the world through the Kambe.

Ethnological Implications

Ethnologically, in Kenya, the gene is now found in ethnic groups in which it was considered to be non-existent a half a century ago. This applies to even deep into the inlands of such groups and not necessarily only at the borders of the initially affected groups. Although macroethnically such individuals are "whatever ethnic group", microhæmatologically and molecularly the individuals are mixed and would better just be referred to as Kenyans. This was evident from the Haematology clinic at Kenyatta National Hospital in Nairobi. We therefore decided to find out the likely true position country-wide and embarked on a survey of SCD in Kenya. This is covered in the next chapter.

Chapter 2

Survey of Sickle Cell Disease in Kenya

Abstract

Although the prevalence of sickle cell trait (SCT) in Kenya was known, the magnitude of sickle cell disease (SCD) was yet to be established. We performed a national survey in all hospitals from November 1987 to May 1990 and found 3605 cases with SCD. Age was recorded for 2821 patients. 77% of these patients were under 15 years of age. The oldest patient was a 50 year old female. The paediatric to adult ratio was 3:1. About 58.4% of the patients were Luo, 23.9% Luhya, 8.5% Mijikenda, 2.7% Giriama, 0.7% Kisii 0.7% Teso, 0.6% Taveta, 0.5% Kalenjin, 0.6% Arab-Negro mixture groups, and 0.2% Kamba. For 2.3% of the 3605 patients, no ethnic origin was traceable. The remaining 0.9% were non-Kenyans from Uganda and Tanzania and a low representation of Kenyans of Kikuyu, Somali, and Turkana origins. There was a discrepancy between SCT rate (SCTr) and SCD rate (SCDr). The Kambes of the Mijikenda group in the Coast Province had the highest SCTr of 35% but a SCDr not exceeding 8.5%, whereas the Luos with a SCTr of 28% had a SCDr of 58.4%. The Kisii with a SCTr of 3% had SCDr of 0.7% whereas the Kikuyu with SCTr's of 2% had SCDr's of 0.2%. There were reports of SCD in the Somali and Turkana, despite the fact that no SCT had been found previously.

Introduction

Sickle cell trait (SCT) is common in malaria endemic lacustrine areas in West and East coastal parts of Kenya [1-2]. SCT rate (SCTr) averages about 25% in the Luos who live around Lake Victoria [3], and ranges from 3% in neighbouring Lacustrine Bantus of the Kisii highlands on the East to an average of 12% in another neighbouring Bantu group in the North, the Luhyas of Western Province. The highest SCTr of 35% was reported from a small division of the Mijikenda group from the East Coast of the Indian Ocean, the Kambe [1]. There is thus a great variability of SCT in various ethnic groups of Kenyans. It is reported to be as low as 1% in the Kamba and 2% in the urban Kikuyu living in Nairobi as well as in the Kipsigis Kalenjin to complete absence in the Masai, Somali and Turkana [1] (Table 1; Fig 2.1)

Table 2.1 Sickle-Cell Trait (Kenya) In the 1950's Foy and Kendall

Race	Tribe	Trial Division	Location	No. Tested	Positive No	(%)
Bantu (North-East, Coastal)	Kikuyu	Fort Hall	Nairobi	67	1	2
	Taita	Dabda	Wesu	127	0	0
	Pare		Taveta	40	2	5
	Chagga		Kibo	75	0	0
	Taveta		Taveta	154	37	24
	Kamba		Machakos	134	2	1
	Nyika	Giriama	Malindi	150	6	11
			Ganda			
		Kambe	Kilifi	39	4	10
			Jaribuni			
		Chonysis	Kaloleni	90	23	26
		Jibanas		119	16	13
		Rabais	Rabai	48	5	10
		Ribe	Ribe	50	13	26
				78	27	35
		Digos	Msambweni	50	11	22
		Durumas	Msambweni	68	7	10
	Pokomos	Ngatan	Garsen	102	27	27
	Boni		Bargoi	81	0	0
	Sanya		Witu	61	0	0
			Add	68	8	12
Bantu (North Kavirondo)	Maragoli			100	-	-
	Bunyore		Kima	100	66	-
	Nyangori		Kapsengeri	44	2	5
	Kitosh		Bungoma	100	21	21
	Kakamega		Kakamega	56	6	12
				46	0	0
	Marama		Butere	100	10	10
	Wanga		Mumias	96	19	20
(Bantu-Nilote	Kisii		Kericho	100	3	3
Bantu (South- East, Coastal)	Makonde		Porto	100	40	40
			Amelia			
			Vipingo	50	2	4
E. Hamites	Maasai	Kaputei	Kajiado	100	0	0
		Lokokelani				
E. Hamites	Maasai	Purko Loita	Narok	82	0	0

Fig. 2.1 Regional distribution of Sickle Cell Trait in Kenya

Note the difference between the Kamba from Eastern Province and the Kambe from Coast Province. Sickle haemoglobin (HbS) is the major ß-globin chain abnormality in Kenya, so that homozygous sickle cell (SS) disease is the major form of SCD here. Earlier studies in East Africa showed virtually no adult cases of SS disease [4-5]. A report by Bwibo and Kasili is available regarding clinical observations on children with SCD in Nairobi [6]. Adults with SS dissease are nowadays regularly seen in various clinics in the country. The mean age of adult SCD patients seen at the Adult Haematology Clinic of Kenyatta National Hospital, Nairobi is 20 years [7]. The extent and natural history of the disease in Kenya was yet to be established [8]. We hereby report the results of a survey we did to estimate the magnitude of SCD in Kenya.

Patients, Materials and Methods

Letters were sent to Provincial Medical Officers (PMO's) with copies to Provincial Hospital Superintendents (PHS's), Provincial Physicians (PPh's), Provincial Paediatricians (PP's), Provincial Pathologists (PPA's), and District Medical Officers of Health (MOH's) about the plan and purpose of the survey. Copies of the same were sent to both Chief Records Officers (CRO's) and Chief Laboratory Technologists (CLT's) at both Provincial and District Hospitals. The letter to the CRO's and CLT's was attached with a questionnaire to record patient data: namely; patient's name, in-out-patient number (IP/OP No.), date of birth (DOB) and/or age, sex, place of birth (POB), ethnic origin or POB of parents or grandparents, date of earliest haemoglobin (Hb) electrophoresis and or sickling test, latest Hb level, and patient's address. The CRO's were advised to pull out records using the International Code of Diseases (ICD) directory. The CRO's were requested to pull out and put aside both in-patient and out-patient files or records of patients recorded as having SCD for review by two researchers later. A few days before

the arrival of the reviewers, the PPh's, PP's, and PPa's were informed by telephone of the intended date of visit to their respective hospitals and the CLT's were requested to have their laboratory records ready for counterchecking.

The whole country was surveyed, with the Provincial Hospital being the point of reference in each of Kenya's eight provinces. The provinces are Central Province, Coast Province, Eastern Province, Nairobi Province, North-Eastern Province, Nyanza Province, Rift Valley Province, and Western Province.

We used the following criteria to enter names on our list from the files of patients diagnosed as having SCD: 1) Hb-elctrophoresis result showing HbS band without HbA band in a patient not transfused within the past 90 days, 2) Hb-electrophoresis showing HbAS bands within 90 days prior to the test in a patient whom either the Paediatrician or Physician confirms symptoms and signs and history of SCD, 3). Evidence of a positive sickling test in a patient with chronic anaemia of around 8 gm/dl and persistent or intermittent scleral jaundice with or without history of vasoocclusive pain crises, given that malaria has been ruled out or the condition persists after successful treatment for proven malarial infection and in the absence of chronic hepatitis. Two research physicians reviewed the records.

Results

A total of 3605 patients with SCD were identified from the hospitals in Kenya's eight provinces. The provincial distribution of the number of patients is shown in Table 1. Age was recorded for 2821 patients of whom 77% were under 15 years of age. The oldest patient was a 50 year old female Nairobi resident who originally grew up in Western Province.

The ethnic distribution was 58.4% for the Luo, 23.9% Luhya, 8.5% Mijikenda, 2.7% Giriama, 2.3% unspecified, 0.7% Kisii, 0.7% Teso, 0.5% Kalenjin, 0.6% Arab-Negro, 0.2% Kamba, and 0.9% other ethnic groups [Table 2.1]. The latter consisted of 21 Ugandans, 12 other Kenyans (5 Kikuyu, 4 Somali, 2 Turkana and 1 Indian), and 1 Tanzanian. The Ugandan patients were 12 Bagandas and 6 Nilotics. Reported SCTr's in these patients' ethnic groups are shown in Table 2.1 Percentage distribution of the patients per province was as follows: 35% in Nyanza, 19.7% in Nairobi, 17.5% Coast, 17% Western, 8.8% Rift Valley, 1% Central, 0.8% Eastern, and 0.2% in N-Eastern [Table2.1], (Fig.2.2). The male to female ratio was 1:1. The paediatric to adult ratio was 3:1. The age frequency distribution pyramid is shown in Figure 2.3.

Discussion

There are over 3000 patients with SCD in Kenya. We might have missed some symptomless cases but SCD in Kenya is of a severe type [9] so that the number of symptomless cases is negligible. The ovarall pediatric to adult ratio was 3:1. The national pediatric to adult ratio is 1:1. With Kenya's at-birth life expectancy of 55 years and a very high population growth rate of 4.1% with a crude live birth rate of 5.1% [10], the child with SCD is still within a high mortality risk group. Survival beyond age 30 is still limited (Fig. 2.3).

Nearly 60 % of the SCD patients were of the Luo tribe. Although the Luos have a SCTr of about 28%, a rate equal to that of some Coastal tribes and even less than that of the Kambes with 35%, [1], the Luos are among the second largest tribe in Kenya with the Luhyas and Kalenjin after the Kikuyu [10]. The Luos constitute nearly half of the population of Nyanza, therefore 35% of patients with SCD in Kenya are from Nyanza (Table 1). The Luhyas from Western Province with 10% SCTr and 24% SCDr are the second largest tribe with SCD. Provincially Nairobi ranks 2nd to Nyanza with a

SCDr of 20%, most patients being Luos and Luhyas. Most patients from Coast Province were of the Mijikenda ethnic mixture of which the Kambe have the 3rd highest SCTr in the world after the Amba in Uganda [11-12] and Simbiti in Tanzania [13]. Only a few Kambe with SCD were ethnically registered.

We observed SCD in ethnic groups in which it had hitherto been thought to be absent (Table 2). Although SCTr's of 1-3% was reported in the Kisii, Kikuyu, Kalenjin and Kamba [1], there have been no reports of SS disease cases in these peoples. Even surprising were reports of Turkana and Somali cases with SS disease (Table 2.2]. SCT was not found in these peoples in earlier surveys [1]. A detailed report of the ethnological implications of SCD in present day Kenya is given elsewhere [14].A few non-Kenyans with SCD were from Uganda and Tanzania (Table 2). Data on SCD are available for both countries [12, 15].

Although we found a few cases with homozygous beta thalassaemia (Cooley's anaemia), we did not find cases with compound heterozygosity for both HbS and ß°-thal or sickle cell ß°-thalassaemia (Sß°thal). Sßthal has been reported from Tanzania [16-17] but the ßthal gene has been considered to be very rare in East Africa [18]. Sß°thal resembles SS disease at alkaline Hb-electrophoresis and needs differentiation by family studies. However, in a survey of over 2000 indigenous Kenyans no case of ß-thal was found [19]. There was no report of sickle cell haemoglobin C (SC) disease. HbC is a rare haemoglobinopathy in East Africa [20-21]. Sßthal and SC diseases, seem to be rare or absent in East Africa, but are common in Central and West Africa from where they have spread to the Americas and Northern Europe [22-23].

Table 2.1: Regional and ethnological distribution of patients with sickle cell disease in Kenya

Ethnic Group, Number and Overall Percentage of Cases by Province

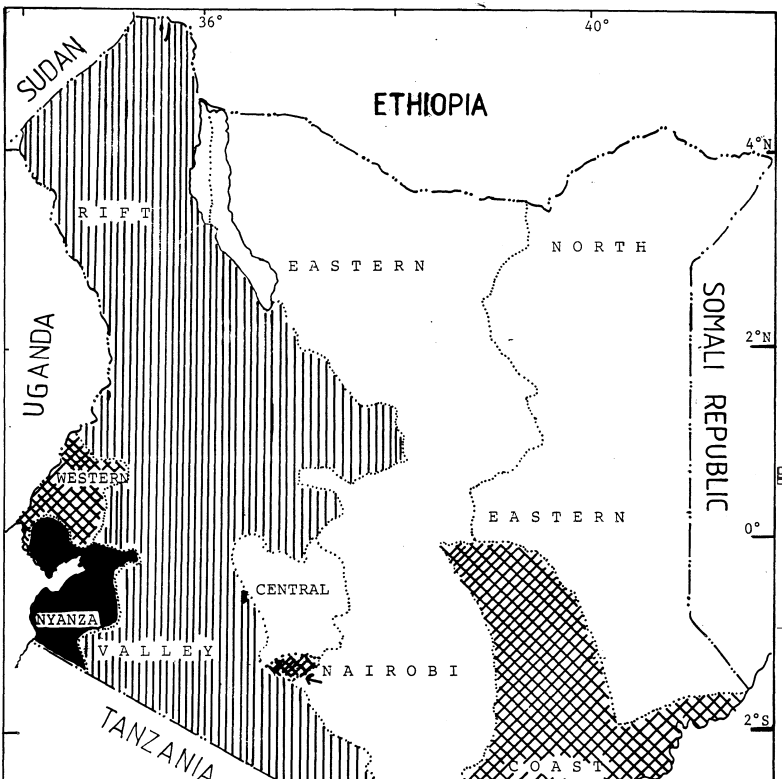
Ethnic Origin	THE PROVINCES								Total (%)
	Nyanza	Coast	Western	Nairobi	RValley	Central	Eastern	NEastern	
Luo	1206	161	27	516	152	27	10	5	2104 (58.4%)
Luhya	25	22	561	130	107	8	8	1	862 (23.9)
Mijikenda	-	296	-	4	3	2	1	-	306 (8.5)
Giriama	-	94	-	2	2	-	1	-	99 (2.7)
Kisii	18	1	-	5	2	-	-	-	26 (0.7)
Teso	1	-	19	1	3	-	-	-	24 (0.7)
Taveta	-	20	-	-	-	-	-	-	20 (0.6)
Kalenjin	-	-	-	-	19	-	-	-	19 (0.5)
Arab/Negro	4	12	-	4	-	-	-	-	20 (0.6)
Kamba	-	3	-	2	-	-	4	-	9 (0.2)
Other	4	5	5	12	5	-	1	2	34 (0.9%)
Unspecified	3	18	-	35	23	-	3	-	82 (2.3%)
Total (%)	1261 (35.0)	632 (17.5)	612 (17.0)	711 (19.7)	316 (8.8)	37 (1.0)	28 (0.8)	8 (0.2)	3605 (100%)

Table 2.2: Sickle Cell Disease in Other Ethnic Groups in Kenya

Ethnic Orign	No. of Cases	Country of Origin	% sickle cell trait (withreferences)	% in resurvey, 1992-2000
Baganda	12	Uganda	19 (11)	-
Nilotic	7	Uganda	28 (11)	-
Kikuyu	5	Kenya	2 (1) (Nairobi)	2 (Mt. Kenya 27
Somali *	4	Kenya	0 (1)	0 (Study incomplete
Turkana *	2	Kenya	0 (1)	1 Lodwar 27
Indian	1	Kenya	? (22)	-
Kuria **	1	Tanzania	28 (13)	-

** No sickle cell trait had been found in these ethnic groups in the 1954 study.*

There was one Indian case of SCD (Table 2) and another case with SCT carrying the HbS from indian ancestors. The true nature of this Indian HbS gene is yet to be established by gene mapping. HbS is reported to be widespread in India [24], where HbD is also found in Gujeratis and Punjabis [25]. HbDPunjab runs the same as HbS at alkaline Hb electrophoresis, therefore in an Indian patient with haemolytic anaemia and a negative sickling test, Hb electrophoresis is necessary for ruling out HbDD disease or HbD-ß°thalassaemia. Two patients had sickle cell haemoglobin OArab (SOArab) disease. The older of the two, now 27 years old has been reported earlier [26]. His 11 year old sister has the same Hb electrophoresis pattern. Inter-ethnic implications of our findings in the survey need further study as well as the natural history of SCD in Kenya. Kenya has reached a stage whereby the diagnosis of SCD no more needs to be based entirely on tribal origin but rather on clinical grounds.



gous Sickle Cell

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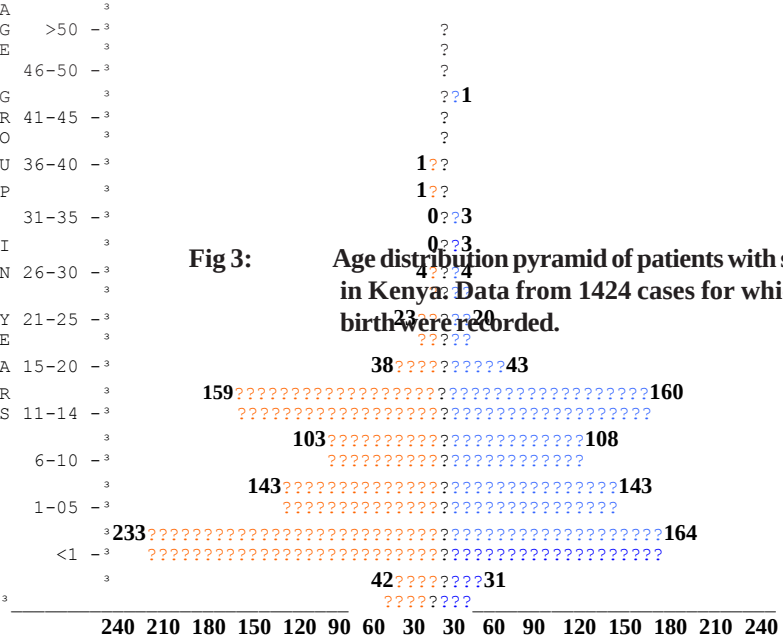


Fig 3: Age distribution pyramid of patients with sickle cell disease in Kenya. Data from 1424 cases for which exact dates of birth were recorded.

Chapter 3

SICKLE CELL ANAEMIA IN KENYA: Its Ethnological Implications from the Kisii Highlands to East of Mount Kenya

Abstract

The Gusii from Kisii highlands, Kalenjins from Rift Valley, Kikuyus of Central highlands, and the Kambas east of the mountain ranges of Kenya are known to have sickle cell trait (SCT) of 3%, 2%, 2%, and 1% respectively, but homozygous sickle cell (SS) disease had not been reported in them. We found SS disease of 1.1%, 0.4%, 0.19%, 0.06%, 0.06%, and 0.06% respectively in the Kisii, Kalenjin, Kamba, Kikuyu, Somali, and the Turkana. No SCT had been reported in Somalis and Turkanas. Luos, Luyhas and Mjikendas with higher SCT rates (SCTr's) indeed ranked highest with SS disease: 54.2%, 24.5%, and 18.9% respectively. Ethnoepidemiologically these findings imply that SCTr's in Kenya had either been underestimated in some ethnic groups or are increasing due to speedy interethnic communication, and that SS disease should be ruled out in any indigenous Kenyans with unexplained haemolytic anaemia. SCTr's need reassessment in Kenya.

Introduction

Homozygous sickle cell (SS) disease in Kenya has hitherto been mainly reported in Luo and Luyha ethnic groups in Western parts of Kenya [1-3]. Although the Mjikenda ethnic groups at the East Coast have sickle cell trait (SCT) rates (SCTr's) ranging from 10-35% [4], there had been no case reports of sickle cell disease (SCD) in them until recently [5]. At the adult haematology clinic at Kenyatta National

Hospital in Nairobi (KNH) we noticed two young adults with SS disease from the Kisii Highlands [6]. SS disease had not been reported in the Kisii whose SCTr ranges from 1-3% [4, 7]. Malaria endemicity is low in Kisii highlands.

The prevailing assumption has been that SS disease does not occur in the Kisii. Our observation prompted us to perform a national survey of SCD and highlight the encounterability of SCD in the ethnic groups in which it was considered to be absent.

Patients, Materials and Methods

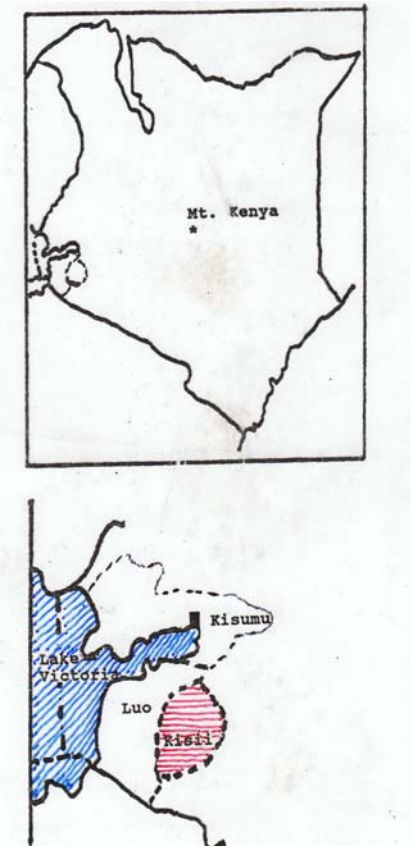
Patients were identified from among ca. 3200 SCD patients of whom data were gathered during a preliminary survey of SCD in Kenya [5]. Pedigrees were traced as far back as possible in patients and/or parents who consented to the exercise. The history was taken either at the haematology clinic in Nairobi or in the patients' home district hospitals. On one occasion, we looked up a patient in the rural area for a pedigree history. All laboratory tests including Hb-electrophoresis were performed at the laboratory in the Department of Medicine, University of Nairobi. Blood samples from the Kisii highlands were preserved in EDTA containers at 4°C for transportation to Nairobi where electronic and conventional evaluation of blood cell indices occurred within 48 hours from the time of sampling. The same applied to Hb-electrophoresis at pH 8.6.

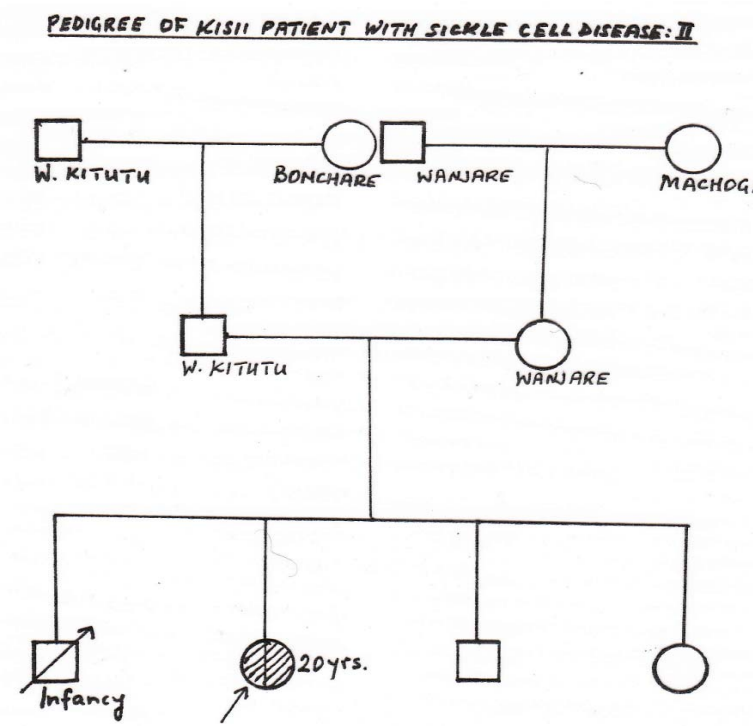
Results

We found SS disease of 1.14%, 0.38%, 0.19%, 0.06%, 0.06%, and 0.06% respectively in the Kisii, Kalenjin, Kamba, Kikuyu, Somali, and the Turkana [Table 1]. Somalis and Turkanas had been found to have no SCT. The Luos, Luyhas and Mjikendas in whom high SCTr's had been reported indeed had the highest percentages of SS disease: 54.16%, 24.55%, and 18.92% respectively.

In two Kisii patients the pedigrees could be traced as far back as possible. This was necessary because the Kisii with 3% SCTr are good neigbours of the Luos with 25 - 28% SCTr [Fig. 1]. No Luo ancestry was apparent in any of the two patients although this cannot biologically be ruled out. Both patients came from Kisii inland and not from the Luo-Kisii border region. A pedigree of one of the Kisii

Figure 1: Map of Kenya showing Luo and Kisii areas in Nyanza





patients is shown in Fig. 2. Other ethnic groups of Kenyans in whom SS disease was reported were Bajunis (0.28 %), Swahili-Arab groups (0.16 %), and Indian (0.03 %) [Table 1].

Discussion

The results of this study show that the prevailing presumptions on the prevalence of both SCT and SS disease among Kenya's various ethnic groups need adjustment. At the time the earlier surveys on SCT were done [4], there were few, if any SS disease patients found

even among the Luos and Mjikendas with very high SCTr's. There was a higher infant mortality rate (IMR) due to various causes when compared to today, and SS disease patients would barely survive childhood even in areas with very high SCTr's. SCD patients now survive to adulthood in Kenya. The mean age for adult SCD patients is 19.6 years [8]. This falls just 3 years below the mean age for 22.7% years of the nation's age group they represent [9].

The assumption that SS disease was non-existent among some ethnic groups like the Kisii and Kikuyu was not entirely wrong, but it would be a matter of time before this view is adjusted. The chances that a Kamba has SS disease are 1 in 50,000, that of a Kikuyu 1 in 250,000 as compared to a Luyha with 1 in 5,000 or a Luo with 1 in 2,000, thus not so much of an issue, but the chance is there!

Whether or not the sickle cell ($ß^S$) gene's presence is a result of focal mutation [10] or secondary spread from another area or ethnic group [11] in Kenya is unimportant. Secondary spread is, however, but not exclusively, the most likely explanation for the presence of the $ß^S$-gene among other ethnic groups in Kenya in which SCT was either scarce or absent. Interethnic communication in Kenya has increased since independence though it was present in precolonial times between indigenous neighbours like Luo-Kisii, Luo-Luyha, and Luo-Kalenjin etc (Figure 1). A perfect example is the mergence of the East coastal nine different subethnicities into the Mjikenda. The Kenyan population has reached a stage where especially young people become uneasy with questions as to which ethnic group they belong. This is especially common among the urban population, which although still constitutes only 10-15 % of the total population, is rapidly increasing. Undue ethnic awareness is fortunately being discouraged in Kenya. Inter-ethinic spread of a hereditary disease like SCD is bound to be enhanced by such policies. However, the very same policies will also enhance dilution of the $ß^S$-gene. Due to gene dilution,

SCTr in American and Carribean blacks is about 8%. This figure must have been higher in the original slaves who were taken to those areas from their African homelands. This fact is demonstrated by the persistence of 17% SCTr in a group of Surinamese blacks who managed to isolate themselves from slavery to the extent of not having much intermingling with non-African blood [12].

Whether the ßS genes in all the Kenyan groups mentioned are identical remains to be established. The Luo-Luyha ßS-gene corresponds to the one that is most common in the Central African Republic [3]. SCD should be ruled out in any indigenous Kenyans with unexplained haemolytic anaemia, especially when other obvious causes like malaria have been ruled out. We have not exhausted all possible explanations, like reports of SCD in the Somali and Turkana in whom no SCT had been found [4]. Kenya has reached a stage whereby the diagnosis of SCD should no more be based on tribal origin

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Table 1: Sickle Cell Disease in Various Ethnic Groups in Kenya. Asterisks Indicate the Tribes among which no Sickle Cell Trait had been detected before

Ethnic Origin	No. of Cases	% of total	% Sickle Cell Trai (& rerences)
Luo	1712	54.16%	25 - 28 [4]
Luyha	776	24.55%	10 - 15 [4]
Mjikenda	598	18.92%	10 - 35 [4]
Kisii	36	1.14%	3 [4]
Kalenjin	12	0.38%	2 [4]
Bajuni	9	0.28	2 [1]
Kamba	6	0.19	1 [1]
Swahili-Arab	4	0.13	2 [1]
Kikuyu	2	0.06	2 [1]
Turkana*	2	0.06	0 [1]
Somali*	2	0.06	0 [1]
Nubian	1	0.03	2 [1]
Indian	1	0.03	? [8]
TOTAL	**3161**	**100**	

?: Place of origin of this patient in India was not known.

Table 2: Regional distribution of sickle cell anaemia patients from the Kisii and Nyamira districts of the Kisii highlands

District	**Hospital**	**Ethnic origin and number of cases**			
		Kisii	Luo	Other	Total
	Kisii	9	6	-	15
Kisii					
	Tabaka	2	4	3	9
Nyamira	Nyamira	6	6	-	12
Total for the 2 districts		**17**	**16**	**3**	**36**

Table 3: Haematology data of three patients of Kisii ethnic origin and one patient of Kamba ethnic origin with homozygous sickle cell disease in Kenya

No	Age (Yrs)	Sex M/F	Ethnic Origin	Hb gm/dl	RBC $x10^{12/L}$	MVC fl	WBC $x10^{9/L}$	RECTICS % *	Genotype CAPE band
1.	21	F	Kisii	9.5	2.88	105	10.5	11	HbSF
2.	16	F	Kamba	8.6	2.79	111	12.4	14	HbSF
3.	17	F	Kisii	8.2	2.77	109	13.1	9	HbS
4.	16	F	Kisii	8.4	2.82	104	15.1	17	HbS

CAPE: Cellulose Acetate Paper Electrophoresis

Chapter 4

Some Clinical and Laboratory Aspects

I. Haematological and Demographic Featurers in Adult Patients With Steady State Homozygous Sickle Cell (SS) Disease in Nairobi, Kenya

Abstract

Sickle cell disease (SCD) in Kenya had been considered a children's disease. We report haematological and demographic characteristics in 147 adult patients with homozygous sickle cell (SS) disease seen at Kenyatta National Hospital, Nairobi, from March 1986 to July 1988. There were 69 males and 78 females with a mean age of 19.6 years (SD 4.3). Only one patient was above 30 years of age. 59% were in the 15-19 year age group. There were no statistically significant differences in mean haemoglobin value and mean WBC count between the sexes. Eosinophilia was noted in two patients with helminthiasis. The mean WBC count was higher than values reported from non tropical areas ($p < 0.05$). Survival of SCD patients in Kenya is still limited to around 30 years of age. The higher mean WBC counts in the tropics is due to increased infection exposure.

Introduction

Sickle cell disease (SCD) patients, especially homozygous sickle cell (SS) disease patients are immunecompromised due to functional asplenia and are prone to infections. Mean white blood cell (WBC) counts have been reported to be higher from studies out of the tropics [1-3] and in children in the tropics [4] and sub-tropics [5] in SS disease patients when compared to controls. We studied red blood cell (RBC) and WBC characteristics in SS disease patients at the adult haematology clinic of Kenyatta National Hospital (KNH) in Nairobi to determine the steady state cut off points for both cell type values and counts and compare with data reported for adult SS

disease patients from non-tropical environments. Patients with SCD who live in non-tropical environments have less exposure to infection risk. Whether there are differences in the blood counts, especially WBC counts between the two groups is not established.

Patients, Materials and Methods

The patient population consisted of 195 SCD patients seen at the adult haematology clinic of KNH from March 1986 to July 1988 who had been identified by cellulose acetate paper haemoglobin electrophoresis. Full sociodemographic data entry was made. Data entry and blood sampling for haematological analysis were not done when the following conditions applied: blood transfusion within the last 90 days, a febrile illness and/or any type of sickle cell crisis within the last 14 days, menstruation at the time of blood sampling in females, and any patient with an active sickle leg ulcer or some other obvious infectious disease. Also excluded were patients under 15 years of age who shuttled between the pediatric and adult clinics. Blood was collected under sterile conditions in EDTA bottles or tubes. RBC and WBC counts and indices were performed using a Coulter Counter S IV plus analyzer in the Department of Medicine Laboratory (DOMLab), University of Nairobi. Counts of reticulocytes (retics) platelets, and differential WBC's were done by conventional methods in the DOMLab. Peripheral blood film (PBF) studies were also performed in the DOMLab and consisted mainly of checking for the presence of: malarial parasites (MP's), normoblasts (nrb's), Howell Jolly Bodies (HJB's), and bizarre RBC forms, especially sickle cells.

Results

Out of the 195 SS disease patients demographic data were incomplete for 10, and 38 were under 15 years of age. Demographic data analysis was performed for the remaining 147 adult patients out of whom 32 did not report for blood sampling. Out of the remaining 115 adult

SCD patients from whom blood samples were taken, 11 reported a recent febrile illness, another 7 had active leg ulcers, 3 were pregnant, 4 were menstruating at the time, 4 had a recent blood transfusion and 2 patients' PBF's were positive for MP's although the patients were symptomless. Data from the remaining 84 patients were entered for haematological analysis.

The age range for all the 147 SCD patients was from 15 to 47 years. Their age group frequency distribution and pyramid is shown in Figure 1. The mean age was 19.6 years (SD 4.3).

Mean values for the electronically determined blood cell indices are shown in Table 1 for the 84 patients with complete haematological data. There were no statistcally significant differences between both sexes. Counts for reticulocytes, normoblasts, platelets, and WBC differntial components are shown in Table 2. These were all within normal range.

Discussion

Although sickle cell anaemia had until recently been considered a children's disease in Kenya, the adult haematology clinic at KNH-Nairobi has records of about 250 young adults and adults with SCD. Among the 147 patients (age range 15-47 years) of whom complete socio-demographic data were available, the mean age was 19.6 years. The adult sickle cell patient population in Nairobi is thus within the reproductive age group. Two of the patients were of Kisii ethnic origin and one was Kamba. Although the Kamba and the Kisii have sickle cell trait rates (SCTr's) of 1 and 3% respectively [6], SS disease had not yet been reported among them. There was also one Bajuni with SCD but most of the patients were of Luo and Luyha origin from Western Kenya as was expected. These observations at our clinic prompted us to do a national survey of SCD in Kenya in order to gain an impression of the prevalence of SCD among various ethnic

groups. The results of the survey are discussed elsewhere [7-8].

Only three (3%) out of the 147 patients in the clinic were aged 30 years and above, one of these being a 47 year old female. The other two (one male and one female) were each 30 years old. Most patients (59%) were between 15 and 19 years of age, followed by 20-24 (28%), and 25-29 (11%), after which there was a sharp drop to 2% (Figure 1). We had no idea whether this was a reflection of the condition of SCD > 15 years of age in the whole country.

Male SCD patients had slightly higher mean Hb, RBC, and MCV values than females but the differences were not statistcally significant [Table 1]. The mean WBC count was higher than that observed by Bwibo and Dawa in children in steady state ($p < 0.05$) from the same hospital [4] and also higher than values observed in non tropical areas ($p < 0.05$) in steady state [1,3,5]. We had hypothesized that this would be the case due to presumed higher exposure to infectious agents when compared to patients with SCD in non-tropical areas, and due to the expected severity of SCD in Kenya from the predominantly Central African Republic (CAR) or Kenya sickle cell gene [9-10]. Data from the PBF (Table 2) showed no major differences between the sexes and only 11% of the studied cases had normoblast counts > 10/100 WBC. It has been suggested [3] that a higher normoblast count of > 10/100WBC might be diagnostic of sickle cell-thalassaemia (Sß^{o} thal). Since we have not yet observed cases with Sß^{o} thal [11] and family studies are not always feasible, this hypothesis need further exploration for easy diagnostic purposes in comparable environments where haemoglobin composition and RBC index studies might not be helpful in differentiating Sß^{o} thal cases from SS disease cases.

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Table 1: Mean blood counts of 84 adults with sickle cell disease seen at Kenyatta National Hospital, Nairobi, Kenya, from March 1986 to July 1988

Haematology Variables	Sex and Mean Haematology Data	
	Males	Females
Hb (gm/dl)	8.9 (2.0)	8.4 (1.4)
Hct (L/l)	29.2 (6.7)	28.3 (6.4)
RBC ($x10^{12}$/l)	3.2 (0.8)	2.9 (0.8)
MCV (fl)	101.4 (5.5)	98.6 (9.2)
Reticulocytes (%)	14.4 (6.8)	14.8 (8.1)
WBC ($x10^9$/l)	15.0 (4.5)	15.3 (7.1)
Platelets ($x10^9$/l)	341.4 (197)	337.0 (99)

No statistically significant differences between males and females ($p > 0.1$)

Table 2: Mean peripheral blood film count data of 84 adults with sickle cell disease seen at Kenyatta National Hospital, Nairobi, Kenya from March 1986 to July 1988

Haematology Variables	Sex and Mean Haematology Data	
	Males	Females
Neutrophils (%)	50.6 (13.0)	51.8 (14.7)
Eosinophils (%	3.6 (4.0)	2.6 (2.8)
Monocytes (%)	4.2 (3.1)	2.9 (3.2)
Lymphocytes (%)	41.0 (12.0)	42.1 (14.1)
Normoblasts (/100WBC)	3.6 (8.4)	4.7 (6.7)

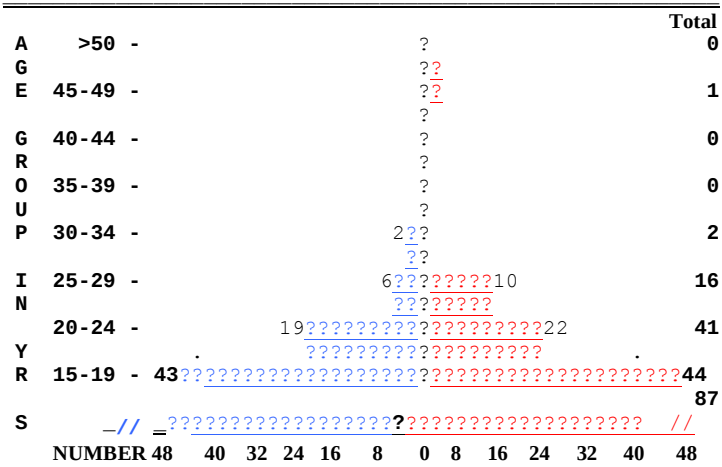

Fig. 1: Age frequency distribution pyramid of 147 adults with sickle cell disease at Kenyatta National Hospital, Nairobi, Kenya from March 1986 to July 1988 (See also Table 3)

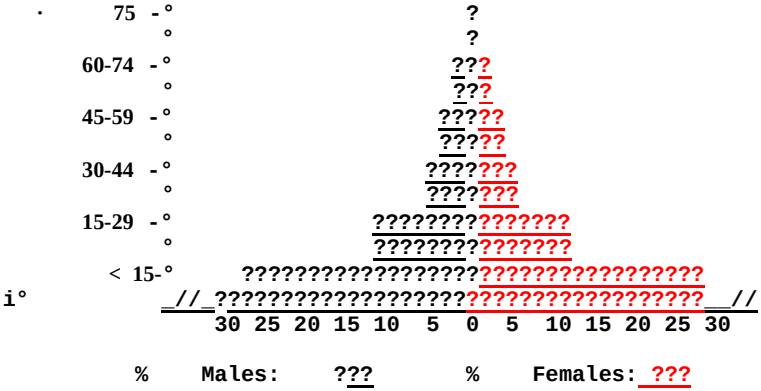

Fig. 2: Age frequency pyramid of Kenya's population in 1987

Table 3: Age Frequency Distribution of Young Adults and Adults with Sickle Cell Disease at Kenyatta National Hopital, Nairobi

	Sex		
Age Group	Males	Females	Both
15	11	14	25
16	4	2	6
17	12	9	21
18	8	11	19
19	8	8	16
20	6	7	13
21	5	3	8
22	4	8	12
23	2	2	4
24	2	2	4
25	1	3	4
26	1	3	4
27	3	2	5
28	1	1	2
29	0	1	1
30	1	1	2
47		1	1
Total	**69**	**78**	**147**

II. Maternal and Foetal Outcome of Pregnant Patients with Sickle Cell Anaemia at Kenyatta National Hospital, Nairobi: A Retrospective Study

Abstract

In a retrospective study we assessed pregnancy outcome in relation to sickle haemoglobin (HbS) and anaemia at Kenyatta National Hospital, Nairobi (KNH) from 1981-1986. There were 36% maternal and 45% foetal losses in sickle cell disease (SCD) pregnants and 7% foetal losses in sickle cell trait (HbAS) from 26 HbS-related pregnancies. Eleven had homozygous sickle cell (SS) disease and 15 had HbAS. Age ranges for both groups were comparable. Mean haemoglobin-level for SS disease patients was 7.8 gm/dl (±SD 1.68), for AS patients 7.8 gm/dl (±SD 2.1). These maternal and foetal losses are quite high. Anaemia alone does not satisfactorily account for the higher losses in SS pregnancies. Other contributory factors need elucidation and intervention.

Introduction

Sickle cell disease (SCD) is a recognized risk factor in pregnancy [1-2]. It is generally thought that this is due to the anaemia. Homozygous sickle cell (SS) disease is the major type of SCD in Kenya, and rates second to malaria as a cause of haemolytic anaemia [3]. SS disease leads to a higher incidence of morbidity and debilitation both through the chronic haemolytic anaemia and vaso-occlusive complications of the haemoglobinopathy. Pregnant patients with SCD, especially SS disease and to some extent sickle cell ß°-thalassaemia are at high risks with respect to both maternal and foetal outcome [1], although reports from other studies [4-5] showed no greater losses in foetal and maternal outcome from SS disease patients when compared to pregnant patients with sickle cell haemoglobin C (SC) disease. We found it needful to assess pregnancy outcome in patients with SCD who are seen at both the Haematology and Obstetrics-

Gynaecology clinics of Kenyatta National Hospital, Nairobi (KNH) when compared to anaemic pregnant patients with sickle cell trait (HbAS). The present report is from a retrospective study.

Patients and Methods

Records were reviewed of both SS disease (HbSS) and HbAS pregnants who delivered at KNH between 1981 and 1986 with the diagnosis of anaemia. HbS status was confirmed by haemoglobin (Hb) electropho-resis. Twenty-six pregnants with anaemia were reviewed, 15 with HbAS and 11 HbSS. Both groups were compared to each other with respect to ethnic origin, age range, haematological indices, gestation period, duration of labour, neonatal birth weight, foetal and maternal outcome.

Results

Total number and age group for the HbSS and the HbAS patients is given in Table 1. All the 26 patients were from the Luo and Luyha tribes from Nyanza and Western Provinces of Kenya. The mean Hb level in SS disease patients was 7.8 gm/dl (±SD 1.68) and in AS patients 7.8 gm/dl (±SD 2.1). The mean WBC count of HbSS patients was 22.01 x 109/l (±SD 10.6) and of AS patients 14.5 x 109/l (±SD 11.0). The mean MCV for SS patients was 99.5 fl (±SD 13.5) and for AS patients 90.1 fl (SD 15.1) [Table 2].

Table 1: Age Group of Pregnant Patients with Homozygous Sickle Cell (SS) Disease and Sickle Cell Trait (HbAS) at Kenyatta National Hospital (KNH), Nairobi: 1981-1986

Age Group in Year	Genotype and No. of Cases	
	SS	AS
15 -20	4	1
21 -30	6	11
31 – 40	1	3
TOTAL	11	15

Table 2: Mean ± Standard Deviation of Haemoglobin (Hb), Mean Corpuscular Volume (MCV) and White Blood Cell (WBC) Count of Pregnant Patients With SS* Disease and HbAS* Seen at KNH* From 1981-1986. In Brackets the Number of Patients from Whom Data were Available

	Genotype and No. of Cases	
Haematology Data	SS (n = 11)	AS (n = 15)
Hb (gm/dl)	7.8 ± 1.68[10]	7.8 ± 2.1
MCV (fl)	99.5 ± 13.5[7]	90.1 ± 15.1[9]
WBC ($x10^9/1$)	22.0 ± 10.6[9]	14.5 ± 11.0[13]

Post transfusion Hb level in SS patients was 8.9 gm/dl (±SD 1.47) and in AS patients 9.3 (± 1.41). Mean gestation for SS patients was 38.2 weeks (±SD 3.86), in AS patients 39.3 (±SD 1.34). Mean duration of labour in SS patients was 10.5 hours (±SD 1.7) and in

AS patients 12.2 hours (±SD 3.5). Mean birth weight of neonates of SS patients was 2583.7 gm (±SD 7.72), of AS patients 2722.3 gm (±SD 593.8) [Table 3].

Four (36%) out of the 11 SS pregnants died peri-delivery [Table 3]. One HbAS patient absconded from follow up. There were four intrauterine foetal deaths together with the four maternal SS deaths and one stillbirth, thus 5 (45%) out of 11 foetuses were lost. Only one (7%) out of the 14 AS pregnancy foetuses was lost [Table 3].

Table 3: Perinatal Outcome of Pregnant Patients with SS* Disease and HbAS* Seen at KNH* Between 1981-1986. Means of Data are ± Standard Deviation. In Bracket the Number for Which Data Were Available.

Perinatal Data	Genotype and No. of Cases	
	SS (n = 11)	AS (n = 14)
Gestation period (weeks)	38.2 ± 3.9	39.4 ± 1.3
Duration of labour (hrs)	10.5 ± 1.6[6]	12.2 ± 3.5[13]
Birth weight (gms)	2583.7 ± 772[7]	2722.3 ± 593
Maternal loss	4 (36%)	0
Foetal loss	5 (45%)	1 (7%)

From this small sample we attempted an age group assessment of maternal and foetal losses as shown in Table 4.

Table 4: Maternal and Foetal Outcome as Related to Age Group in Pregnant Patients with SS* Disease at KNH* in the 1981-1986 Period

Age Group (Yrs)	No. of Cases	Maternal Loss	Foetal Loss
15 – 20	4	1	2
21 – 30	6	3	3
31 – 40	1	-	-
TOTAL	11	4 (36%)	5 (45%)

Discussion

Most patients were from Siaya district in Nyanza Province and Kakamega district in Western Province. One of the HbAS patients absconded from follow up. The age range in both groups was comparable. The age group 21-30 years was best represented in both genotypes, but in the age group 15-20 years the SS disease group dominated [Table 1].

Although the figures are too small for statistical comparisons, it seems that anaemia in pregnant HbAS patients presents at a later age. The mean Hb-level was equal in both groups both before and after blood transfusion. This similarity might have been predetermined by the matching of HbS and anaemia to pregnancy, but we would expect the Hb-level of HbAS pregnants to be significantly higher than that of HbSS pregnants. The cut-off point for Hb-level of HbAS pregnants needs assessment. The WBC count and MCV level were higher in SS disease than HbAS patients [Table 2], but the differences were not statistically significant in the small sample of patients. It seems that anaemia in the HbAS pregnants was not due to chronic haemolysis.

Anaemia alone does not explain the high maternal and foetal losses in SS pregnancies as compared to AS pregnancies. Some other factors probably share responsibility for the losses. HbSS pregnants have pre-existent risk factors like a higher HbS content with relative hypoxia when compared to HbAS pregnants with the same Hb-levels. However, blood transfusion should have corrected the difference. Labour might

masquerade a non-haemolytic sickle cell crisis in a HbSS pregnant, thereby adding a potential mortality risk especially to the mother and thereby to the foetus. It has however, been noted in other studies that some pregnant SS disease patients do quite well [6]. Regular and proper perinatal care is mandatory especially for the HbSS pregnants. Both SS disease and HbAS females should be included in genetic counselling and family planning programmes to prevent both the spread of HbS genes and birth of patients with SCD. When and where praenatal diagnostic methods are available, potential parents of SS disease patients should be informed of the procedure. Whether or not they want to use it is their own choice. A typical case is the oldest one in our sample [Table 4] who at 32 years of age defied all advice on genetic counseling and proceeded with pregnancies. One would say that she was "lucky" up to her 3rd gravidity. She was later lost to follow up.

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Chapter 5

DIAGNOSIS OF SICKLE CELL ANAEMIA IN LOW INCOME REGIONS: The Presence of Sickle Cells in the Peripheral Blood Film Specificity and Sensitivity of Diagnosis of Homozygous Sickle Cell Disease in Kenya

Abstract

The final diagnosis of sickle cell disease (SCD) is established by haemo¬globin (Hb) electrophoresis, but the test is expensive and absent in most hospitals in Kenya. We studied sensitivity, specificity and cost effectiveness of the peripheral blood film (PBF) in diagnosing sickle cell anaemia (SCA), the most common type of SCD in Kenya. The PBF can be done even in health centres and dispensaries provided there is a good microscope and a good laboratory technician. The study was performed in SCA endemic Western Kenya in 767 subjects in 12 months. Hb level, WBC count, PBF, sickle cell test (SCT) and Cellulose Acetate Paper Electrophoresis (CAPE) were performed. In the PBF, presence of sickle cells was pathognomonic for SCA. SCA was found in 21, sickle cell trait in 120, and normal genotype in 616 subjects. Sensitivity of the PBF versus SCT and CAPE to detect SCA was 76% with a specificity of 99.7%. The PBF was cheaper than both methods by 31.1 %.

Justification of the Study

Although the final diagnosis of sickle cell disease (SCD) is established by haemoglobin (Hb) electrophoresis, the equipment for Hb-electrophoresis is expensive and usually unavailable or incomplete in major referral hospitals and virtually absent in district hospitals in Kenya. SCD is a major health problem in Kenya, especially in the

Lake and coast regions 1,2. Most references recommend Hb-electrophoresis for confirmation of the diagnosis 3 6. The reason for this is simply that most of these are written from countries where compound heterozygous forms of SCD exist, so that haemoglobin separation by Hb electrophoresis becomes mandatory. It is also known that certain conditions can lead to false positive 7 8 or false negative 9 10 sickle cell test (SCT), however, these can be easily overcome by appropriate procedures.

It was important to device an accurate but cheap method of establishing the diagnosis of homozygous sickle cell (SS) disease which is the most common type of SCD in Kenya. The cheapest method which can be performed even in rural health centres is the peripheral blood film (PBF). This method had not been systemati¬cally established as a reliable and cost effective way to diagno¬se SS disease in developing countries, especially the areas where SS disease is the most prevalent form of SCD. Our study aimed at establishing cost effective specificity and sensitivity of this method.

Materials and Methods

The study was carried out at Nyanza General Provincial Hospital, Kisumu together with a study on prevalence of malaria in patients with sickle haemoglobin (HbS). Blood samples were taken from indigenous Kisumu District residents who presented at the out pa¬tient clinic with what was thought to be malaria. Name, age and sex were recorded. For each case the following tests were done: Hb, PCV, WBC count; PBF for: RBC morphology especially sickle cells, and malarial parasites; and Hb-electrophoresis. Blood was drawn in sterile EDTA tubes or bottles and PBFs were stained in the usual manner. WBC and RBC counts and indices were done by the Coulter counter. The technicians taking blood samples were different from the technicians doing SCTs, PBFs, and Hb-electrophoresis. The study period was 12 months. All data were

entered in the computer for analysis. Specificity and sensitivity of the PBF was compared to that of the SCT and Hb electrophoresis using likelihood ratios. Cost effectiveness analysis was based on consumable material values, technicians' time and workload, and non consumable equipment investment.

Results

Blood samples were taken from 773 subjects in a period of 12 months. Out of these, Hb electrophoresis could not be performed in 6 cases, 5 cases were < 6 months of age, and 5 other cases were non indigenous residents. Data were analysed for 757 cases.

There were 353 males and 404 females so that the male to female ratio was approximately 1:1. Twenty-one patients had SCA, 120 HbAS, and 616 the normal HbAA genotype. In each group, the children (age group < 15 years) were 18 (85.7 %), 48 (40 %), and 229 (36.6 %) respectively. Table 1 shows the PBF as compared to the SCT and Hb electrop¬horesis in diagnosing SCA, HbAS and HbAA genotypes in the 757 Kenyans. Genuinely `false negative' PBF for HbS was observed in a two year old child with HbSF and foetal Hb (HbF) on cellulose acetate paper electrophoresis (CAPE) whose Hb was 9.5 gm/dl and a 33 year old female with most likely Hb Kenya (Table 1) whose Hb was 12.3 gm/dl. The sensitivity of the PBF was 86.4%, its specificity 98%, positive predictive value (+PV) 90.5% and negative predictive value (-PV) 97.5% (Table 2). The PBF of HbSS versus both HbAS and HbAA cases as should be the case, had a sensitivity of 76% with a specificity of 99.7% and unchanged PV values (Table 2). Table 3 and the figure show cost effectiveness comparison of the PBF versus the two other methods.

Discussion

Although Hb electrophoresis is the gold standard for diagnosis of sickle cell and other haemoglobinopathies, it is expensive in Kenya

where also Provincial hospitals find difficulty in maintaining the procedure. Transportation of blood samples from district hospitals to provincial centres and then from there to Nairobi for Hb electrophoresis has proven to be very difficult and expensive. The need to establish as cheap and more feasible way to diagnose SCD in the rural setting, particularly in areas where SCD is endemic, was therefore imperative.

Compound heterozygous forms of SCD like sickle cell beta thalassaemia (Sâthal) and HbSC disease are rare in Kenya. They could be difficult to identify with a PBF alone except for Sßthal without HbA production (Sâ?thal) where the HbS content usually exceeds 60%, a condition which is conducive to in vivo sickling. In all other compound heterozygous forms of the disease, the HbS content is around 50%. The other haemoglobins, even if abnormal, interfere with in vivo sickling. The PBF of such patients will be negative for sickle cells as was seen in a two year old girl with a positive SCT and HbSF bands on CAPE (Table 1). She most likely had SCA with a HbF content still high, enough to prevent in vivo sickling. The other case with HbS like movement on CAPE (Table 1) but negative slides for sickle cells on both PBF and SCT was a 33 year old female with most likely Hb Kenya11. The only other haemoglobin which would show a similar behaviour in Kenya is HbDPunjab, however the patient was a black West Kenyan who was very unlikely to be homozygous for the haemoglobin2. In Kenya where 99% of SCD cases are SCA with HbS content of > 70%2,12, the diagnosis of SCA with a PBF is cheap, relatively sensitive and specific, and should be recommended for use in rural health facilities which have laboratories.

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Table 1: The peripheral blood film as compared to the sickle cell test (SCT) and Hb electrophoresis in diagnosing homozygous sickle cell (SS) disease, sickle cell trait (AS), and normal genotype (AA) haemoglobins in 757 West Kenyans

Diagnostic Test	Sickle Cells Present			Sickle Cells Absent		
	AA	AS	SS	AA	AS	SS
Peripheral Blood Film	3	3	19	613	117	2*
Sickling Test	0	120	20	616	0	1†
Hb-Electrophoresis	0	120	21*	616	0	0

*One of these had HbS and HbF bands on CAPE and was 2 years old, the other one is the same that also had a negative SCT, †and most probably had Hb Kenya.

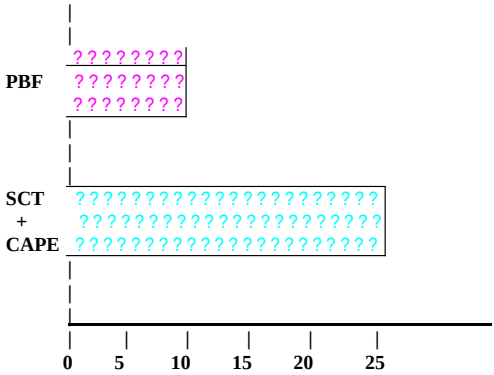

Fig. 1. Cost effectiveness of the peripheral blood film (PBF) vs sickling test (SCT) and cellulose acetate paper electrophoresis (CAPE) in the diagnosis of sickle cell anaemia in Kenya

Cost for tests performed in the (x 10,000 Kenya Shillings

TABLE 2: Sensitivity and specificity of the peripheral blood film in diagnosis of homozygous sickle cell (HbSS) disease in Kenya: Comparison of the peripheral blood film (PBF) versus (vs) sickle cell test and cellulose acetate paper Hb-electrophoresis to detect A: HbSS vs sickle cell trait (HbAS), B: HbSS vs normal genotype (HbAA), and C: HbSS vs both HbAS and HbAA. Positive (+) and negative ( ) predictive values are also show

A		B		C	
SC^{S+}	SC^{S-}	SC^{S+}	SC^{S-}	SC^{S+}	SC^{S-}
SS 19	2	SS 19	2	SS 19	2
AS 3	117	AA 3	613	AA+AS 6	730

Sensitivity: $\frac{19 \times 100}{22} = 86.64\%$

Specificity:

+Predictive Value:

Predictive Value:

Table 3: Cost effectiveness of the peripheral blood film (PBF) vs sickling test (SCT) and cellulose acetate paper Hb electrophoresis (CAPE) in diagnosing homozygous sickle ce1l disease in Kenya. Prices show costs of minimum purchases of both consumable materials and non-consumable equipment and not necessarily the cost of this study.

*Unit time a technician spends on each test paid out on an 8 hour work day subsistence basis.

Chapter 6

MALARIA AND THE SICKLE CELL GENE: A STUDY IN WESTERN KENYA: Higher Resistance to Plasmodium Falciparum Infection in Patients with Homozygous Sickle Cell Disease in Western Kenya

Abstract

Sickle haemoglobin (HbS) is considered to be protective against malaria. Malaria is considered to be fatal in homozy¬gous sickle cell (HbSS) disease. In a cross sectional survey of 766 residents of Western Kenya near Lake Victoria by alka¬line Hb electrophore¬sis, 20 had HbSS disease, 120 had sickle cell trait (HbAS) and 626 the normal genotype (HbAA). Blood slides for malarial parasites (MP's) were performed in 728 cases: i.e. 592 HbAA's, 116 HbAS's, and all the 20 HbSS's. Malaria was found in 261 HbAA's (35.8%), 42 HbAS's (5.8%), and 4 HbSS's (0.5%) of all the cases. Genotypically malaria preva¬lence was 44.1% among the HbAA's, 36.2% among the HbAS's, and 20% among the HbSS's. The relative risk of malarial infection was 0.33 in the HbSS's as compared to both HbAA's, and HbAS's. The protection conferred by HbS against malaria is more marked in HbSS disease than in HbAS.

Introduction

Homozygous sickle cell (HbSS) disease and malaria are both major health problems in Kenya and are both respectively responsible for hereditary and acquired haemolytic anaemias [1-2]. Sickle haemoglobin (HbS) is considered to be protective against malaria [3-5]. This is why HbS is prevalent in malaria endemic areas (MEA).

Although reports regarding data on malaria and sickle cell trait (HbAS) are conflicting [6], and reports from Africa on parasite densities have been inconsistent [7-8], it is hypothesised that HbSS disease patients are at risk for increased morbidity [9-10] and even mortality [8, 11-12] from malaria. That is why such patients in MEA are put on antimalarial chemoprophylaxis throughout life. We performed a study to establish HbSS disease as a risk factor in malarial infection in an indigenous HbSS population in MEA that is considered to be semi immune to malaria.

Materials and Methods

The study population was West Kenyan residents of Kisumu area, a region considered to have up to 28% HbAS. All indigenous patients attending the the blood testing laboratory to rule out malaria and who had resided in the area for at least 6 months or had migrated from a equally malarious area were included in the study. Any otherwise cases including babies < 6 months old were excluded from the study. This was a descriptive cross-sectional study.

A history of fever and of antimalarial drug use at the time of blood sampling was elicited and noted down together with patients' age, sex and place of residence. Blood samples were drawn under sterile conditions in EDTA bottles. In each case, Hb level, peripheral blood film (PBF) for malarial parasites (MP's), and Hb-electrophoresis were performed. All data were entered in the computer for analysis. The $?^2$ statistic was used to compare proportions and student's t-test to draw correlations where applicable.

Results

Blood samples were taken from 773 subjects in a period of 12 months. Out of these, Hb electrophoresis could not be perfor¬med in six cases. One of the remaining 767 cases had Hb Kenya. Blood film for malarial parasites were not done in another 39 cases.

The results on socio demographic and genotypic data of the 766 cases are shown in Table 1. Blood slides for malarial parasites (MP's) were performed in 728 cases: i.e. 592 HbAA's, 116 HbAS's, and all the 20 HbSS's. Malaria was found in 261 HbAA's (35.8%), 42 HbAS's (5.8%), and 4 HbSS's (0.5%) of all the cases (Table 2). Incidence of malaria by genotype is shown in Table 2 and Fig 1. Per genotype the prevalence of malaria was 44.1% among HbAA's, 36.2% among HbAS's, and 20% among HbSS's (Fig 2). The risk of getting malaria by the HbSS's was < 0.33 as compared to the other two genotypes (Table 3).

Discussion

The relationship between malaria and the sickle cell gene has led to extensive research but has remained controversial [6]. Our hospital based study in an area which is endemic for both malaria and HbS seems to confirm the hypotheses and findings that the sickle cell gene indeed protects against malaria [3-5] and that such protection is most likely related to HbS levels. This should explain how, contrary to clinical expectation, HbSS cases in our study have less malaria than HbAS and HbAA cases in that order. It is possible however, that non-HbS related genes or factors also account for this protection [13]. Alpha thalassaemia (a thal) for example has been shown to offer resistance to malarial infection [14] and has also been shown to co-exist with HbS in Western Kenya [15]. We did not however perform a-globin gene mapping. Neither did we check for glucose 6 phosphate dehydrogenase (G-6=PD) deficiency. G-6-PD deficiency has been implicated in resistance to P. falciparum [16].

Sickle cell trait among the study group is only 15.6% as opposed to the expected 25 28% however the study did not only select for the indigenous Luo ethnic group with such high HbS rates. The spread of the HbS gene has, however, been noted among ethnic groups that initially did not have the gene in Kenya [1].

Conlusions from the observations in this study are: 1. that resistance to P. falciparum is genotypically HbS level ralated, 2. that other genetic factors may concurrently or singly play a role in the resistance and 3. that where malaria and HbS are coendemic, a relatively higher proportion of patients with HbAA will report for treatment for clinical malaria.

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Table 1: Age group, sex, and genotype of 766 West Kenyan patients entered in the study of homozygous sickle cell (HbSS) disease as a risk factor in malari¬al infection in Kenya. The other genotypes are sickle cell trait (HbAS) and normal haemoglobin A (HbAA)

Age Group	Sex	Genotype			Totals
		AA	AS	SS	
≤ 15 Years	Males	126	25	11	162
	Females	103	23	6	132
> 15 Years	Males	150	23	0	173
	Females	205	40	2	247
Unknown	Males	12	6	0	18
	Females	30	3	1	34
		626	120	20	766

TABLE 2: Incidence of malaria by genotype in 728 West Kenyan patients in the study of HbSS disease as a risk factor in malarial infection. In brackets the % prevalence of malaria.

Genotype	P. Falciparum Present	P. Falciparum Absent
Hb SS	5 (0.7)	15 (2.1)
Hb AS	42 (5.8)	74 (10.2)
Hb AA	261 (35.8)	331 (45.5)
TOTALS	307 (42.2)	421 (57.8)

Table 3 Relative risk (RR) of the HbS gene in malarial infection in 20 patients with HbSS disease and 120 cases with HbAS as compared to 592 cases with HbAA genotype in Western Kenya. Odds ratios (OR) and p-values are shown

Genotype	Mal +	Mal --
SS	4	16
AS	42	74

Genotype	Mal +	Mal --
SS	4	16
AA	261	331

$$\text{OR} = \frac{4 \times 74}{42 \times 16} = 0.44 \qquad \text{OR}$$

$$PR = \frac{0.55(0.22 < RR < 1.37)}{p > 0.1} \qquad RR = \frac{0.45(0.19 < RR < 1/10)}{p < 0.05}$$

GENOTYPE	MAL +	MAL –
AS	42	74
AA	261	331

GENOTYPE	MAL +	MAL –
SS	4	16
AS / AA	303	405

$$OR = \frac{42 \times 331}{261 \times 74} 0.72 \qquad OR = \frac{4 \times 405}{303 \times 16} = 0.33$$

RR = 0.82 RR = 0.47

p > 0.1 p < 0.05

Table 4: Relative risk (RR) of the HbS gene in malarial infection in 20 patients with HbSS disease and 120 cases with HbAS as compared to 592 cases with HbAA genotype in Western Kenya. Odds ratios (OR) and p-values are shown. The presence of malaria (MAL+) and absence of malaria (MAL-) are compared in clusters of HbSS versus HbAS (A), HbAS versus HbAA (B), HbSS versus HbAA (C) and HbSS versus both HbAS and HbAA (D)

Cluster	Genotype	Mal +	Mal –	Relative Risk	Odds Ratio	P-Value
A	SS	4	16	0.55	0.44	>0.1
	AS	42	74			
B	AS	42	74	0.82	0.3	>0.1
	AA	261	331			
C	SS	4	16	0.45	0.3	<0.05
	AA	261	331			
D	SS	4	16	0.47	0.33	<0.05
	AS / AA	303	405			

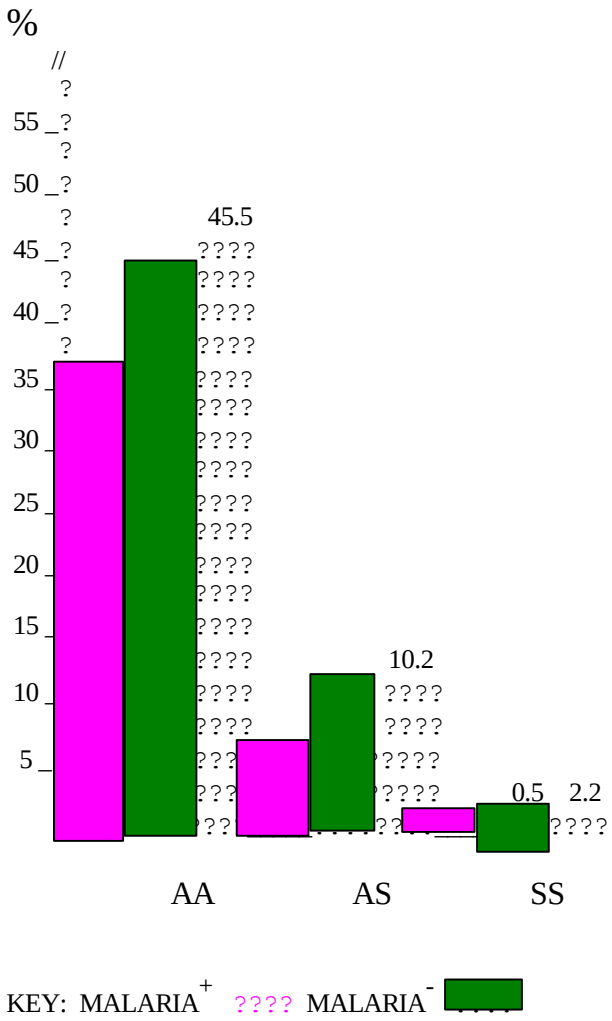

Figure 1: Percentage distribution of P. falciparum infection in 728 West Kenya residents according to genotype

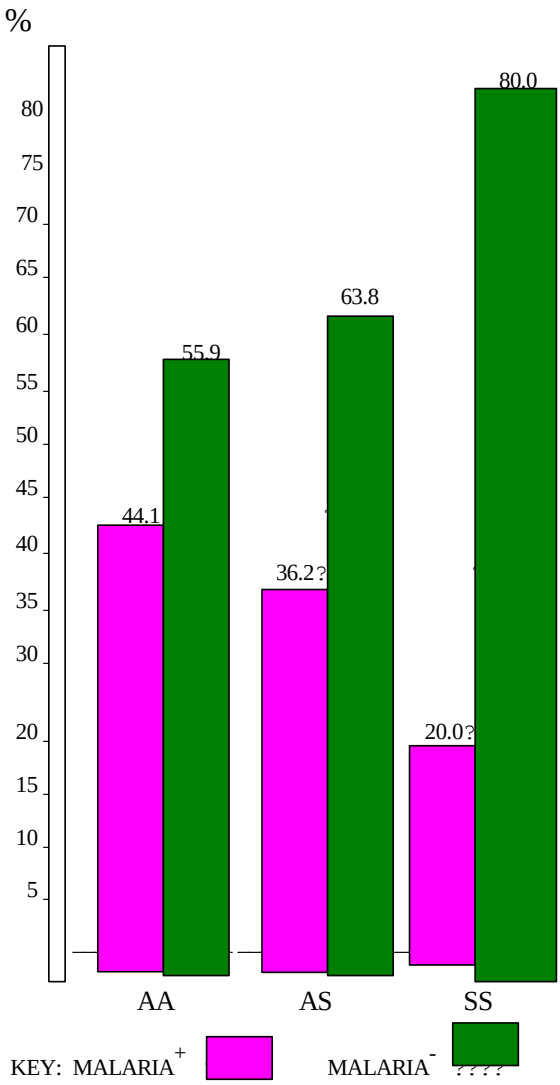

Figure 2: Percentage distribution of P. falciparum infection in 728 West Kenya residents per genotypic group

Chapter 7

MANAGEMENT OF SICKLE CELL DISEASE: Current Concepts in the Treatment of Sickle Cell Disease

(Reproduced and updated by permission from PhD thesis and Trop Geogr Med 1983; 35:105-110)

Summary

The treatment of sickle cell disease (SCD) is still primarily symptomatic. However, there have been major advances in understanding the pathophysiology of sickling syndromes. This in turn has led to a proper approach in the management of the sickle cell patient. A summary of the regimens are presented here as we best understand them today.

Introduction

Although the molecular aberration in SCD was described by Pauling [1] in 1949, the clinical aspects of the disease were described earlier by Herrick [2] in 1910. The molecular and clinical entities of the disease are largely defined, but the management remains disappointing. The major manifestations of the disease are the chronic haemolytic anaemia and the sickle cell crises, especially the painful crises. Sickling is triggered by a drop in oxygen tension and by acidosis. Treatment aims at preventing, arresting, or reversing the pathophysiologic processes in the sickle erythrocyte which lead to clinical symptoms and syndromes.

The treatment of SCD consists of symptomatic treatment of the anaemia, management of the sickle cell crises, management of chronic complications in steady state, management under some special conditions, and prevention of the sickle cell crises.

Symptomatic treatment of the anaemia

The anaemia is chronic and haemolytic in nature. Most patients adapt to their anaemia and do fairly well in steady state. Iron suppletion is unnecessary and even dangerous unless concomitant iron deficiency anaemia has been confirmed, espe¬cially in young children [3]. The hypothesis that concurrent iron deficiency anaemia in these patients may be advantageous lacks clinical proof [4].

Iron suppletion in SCD patients will lead to iron overload. Folic acid suppletion is the logical approach in this condition but is still disputable. Serjeant (personal communication) has not found any haematological benefit by folic acid suppletion in Jamaican patients with sickle cell anaemia; folate deficiency is not outspoken in Jamaica. It seems reasonable to limit the use of folic acid to areas where a dietary deficiency may exist also in the general population. Like iron, blood transfusion should not be routinely used in SCD patients who are in steady state.

Treatment of sickle cell crises

An understanding of the different kinds of sickle cell crises is necessary in order to make a correct clinical approach to treatment. There are three major forms of sickle cell crises: the anaemic sickle cell crises, the vasoocclusive painful sickle cell crises, and the non-anaemic non-painful vasoocclusive sickle cell crises.

The anaemic sickle cell crises manifest in three forms: acute haemolytic exacerba¬tion crises, aplastic crises and acute splenic sequestration syndrome (ASSS).The ASSS should be suspected in all children less than 5 years with all forms of the disease and in older children and adults with either sickle cell haemoglobin-C disease or sickle cell ß-thalassaemia disease. In the treatment of this group of patients with the anaemic crises, blood transfusion should be considered and may defray fatality. In endemic areas, malaria should

be considered in all groups of patients but especially in the group with a haemolytic exacerbation. Rehydration as mentioned under painful crises should be instituted when necessary. The painful sickle cell crises are major presentations, usually comprising bone infarction, visceral organ infarction and priapism. Bone infarction in young children may manifest as a typical clinical picture known as the hand-foot-syndrome. It may present with vague symptoms in older children, young adults and adults. A careful history taking and physical examination will usually reveal it to be local. Bone crises can present as acute arthritis.

Visceral involvement may include infarction of the spleen especially in all children under 3 years of age and in older children and adults with either sickle cell haemoglobin-C disease or sickle cell ß+-thalassaemia. Painful visceral involvement can also occur in the liver, lungs and other visceral organs. Priapism is an obnoxious painful complication in SCD.

The painful sickle cell crises need analgetic and hydrative therapy. Before starting the treatment the crisis should be properly assessed. The pain should be severe and of recent onset, preferably less than 12 hrs duration, unrelieved by oral analgesics. The patient is afebrile or has only a mild fever. A physical examination should rule out acute pulmonary or abdominal pathology, or possible infective or inflammatory conditions, and the white blood cell (WBC) count is below 20.000/cmm. Blood should be drawn for electrolyte and haematological tests. Analgesia with 50 mg meperidinc hydrochloride (Demerol, Pethidine) and 25 mg promethazine hydrochloride (Phener¬gan) intramuscularly, should be given and repeated if and when pain returns but not it less than 3 hours. Intravenous fluid should be started with 5% dextrose at a rate of (ml/kg/hr; this is about 300 ml per hour for a 50 kg subject. Supplements (NA+, K+

Cl-) can be added to this intravenously as indicated by the laboratory results. One should check for circulatory overload and urine output. Many patients will be improved and able to return home after 2-3 liters of fluid is given at this rate. A few will need further observation and treatment over a 24 hi period (Treatment protocol, Comprehensive Sickle Cell Center, Medical College o: Georgia, Augusta, USA).

Controlled double blind clinical trials [5-7] could not confirm the effectiveness o alkali in the treatment of painful sickle cell crises. Success with oxygen in not controlled trials is not clear [8, 9]. However, acidosis and hypoxaemia in these patient should be treated in the conventional manner. Surgical intervention may be necessary, when hypersplenism quickly eliminates transfused blood and in non responding priapism [10].

The non-anaemic, non-painful crises include central nervous system involvement, principally manifesting as cerebrovascular accident, vitreous humour haemorrhage and painless haematuria. Painless haematuria is also encounterered in persons with sickle cell trait. Whenever and wherever possible, these patients need hospital observation. Hydration should be instituted as in painful crises. Specialists should be consulted when necessary.

The benefit of blood transfusion in cerebrovascular crises should be considered [11] but reports of double blind controlled trials are not available. Lntransigent haematuria resulting in a further drop of the haemoglobin level justifies blood transfusion in patients with SCD. Epsilon aminocaproic acid (Amicar, Caprolest) should be given at a loading dose of 5 g., followed by one gm. per hour until bleeding stops. Amicar can be given either intravenously or orally, the dosage not exceeding 30 gm in 24 hours. Rapid intravenous administration should be avoided to prevent hypotension, bradycardia and other arrythmias [12, 13]. Unrelenting haematuria poses a great problem

(nephrectomy!) since haematuria may later occur in the other kidney.

As a general guideline, use the following steps when managing sickle cell crises:

If the patient is ill enough or in sufficient pain to need admission:

1. Ensure adequate and regular analgesia (usually s/c or oral morphine or diamorphine, or Tramadol, do not use pethidine)
2. Keep warm.
3. Ensure high fluid intake (oral if possible but i/v if necessary). Do not restrict oral fluids as long as bowel sounds are present unless there is evidence of intestinal obstruction.
4. Consider the chest syndrome. Chest pain (T-shirt distribution), breathlessness, crepitations or signs of pulmonary consolidation. Check pulse oximetry ± blood gases if in doubt. Remember: acute sickle chest syndrome is the major killer of these patients.
5. Consider the girdle syndrome. Girdle pain, abdominal distension (without rebound) and absent bowel sounds. Basal consolidation.
6. Monitor liver and spleen size and compare to notes for steady state size.
7. Search for infection or other treatable condition (including blood cultures, MSU and a chest X-ray if indicated).
8. Check if the patient is taking penicillin regularly. If not, consider iv ceftriaxone to cover pneumococcal and/or haemophilus infections.
9. Carry out blood count and reticulocyte count alternate days until condition has stabilised.

10. Group and save (cross match if Hb reticulocytes have fallen by more than 25% of normal for that patient.

11. Consider initiation of some or all these whilst the patient is still in A & E.

12. Contact the Haematology Registrar/Consultant on duty.

Management of chronic complications in steady state

Chronic complications related to SCD include cholelithiasis (bilirubine stones), avascular necrosis of the femoral head (ANFH), sickle cell retinopathy, sickle cell nephropathy, and leg ulcers.

The enthusiasm with which SCD patients with gall bladder stones are referred to the surgeon should be tempered. Complications of cholelithiasis (pancreatitis and gall bladder cancer) as seen in the general population with cholelithiasis have not been encountered in patients with SCD [14]. These patients are usually younger in comparison with cholelithiasis patients in the general population and they have bilirubine stones.

A SCD patient with an acute abdominal visceral crisis (liver!) who shows gall bladder stones on an X-ray poses a dilemma to the physician or paediatrician, especially when there is accompanying fever, which is not uncommon in these patients. The best thing to do in such a situation is first follow the treatment procedure outlined for crises and at the same time notify the surgeon in case a laparotomy will be inevitable. Sickle cell nephropathy, ANFH, and retinopathy need concomitant care in the respective specialist fields. Care should be taken that these patients are not tossed from hospital to hospital or from physician to physician. Leg ulcers should be treated in the dermatologic clinic but the most important part of management is proper instruction of the patients in hygienic prevention of secondary ulcer infection and concerning the need for bed rest.

Management under some special conditions

Three major special conditions need careful attention in these patients: pregnancy, surgery and anaesthesia. Detailed discussions on these subjects are beyond the scope of this write up. Although pregnancy was originally considered not worth the risk in these patients [15], the general experience now is that with proper care, pregnancy carries less somber risks than was formerly noted [16]. These should be proper cooperation between the gynaecologist-obstetrician and the physician-haematologist. Prophylactic blood transfusion in pregnant women with SS disease reduces both maternal and foetal risks to that of pregnants with sickle cell trait [17]; transfusion is advisable from the second trimester of pregnancy in patients with sickle cell anaemia and sickle cell ß°-thalassaemia. The regime to be followed depends on haematological laboratory follow-ups and should be determined from case to case.

Any surgery necessitating general anaesthesia is hazardous in these patients and may carry greater risks in hospitals and areas where both surgical and anaesthesiolo¬gic facilities are not well advanced. General anaesthesia should only be applied when imperative. However, current advances in anesthesiology have largely minimized such risks. Prophylactic transfusion with 15-20 ml packed red cells per kg of body weight the evening before surgery [18] is preferable to a two volume exchange transfusion given 10-15 days before surgery [19]. Anaesthesia should be introduced with 100% oxygen during the first 5 minutes. Proper oxygenation should be maintained during the operation and thereafter until the patient is well conscious. The systolic pressure during surgery should not be less than 90 mm Hg. The use of a warm blanket during surgery should prevent cooling [20-21]. Tourniquets should not be used too long.

Prevention of the sickle cell crises

Situations that can induce the crises should be avoided. Hypoxic conditions and situations leading to acidosis must be prevented. Exposure to extreme cold should be discouraged. In warm climates especially the tropics the patient should be guarded against dehydration. This applies also to patients in all types of climates, especially children. Enough fluid intake should be encouraged. Substances that can induce acidosis like acetazolamide (Diamox) should be avoided. Caution is needed against substances that can trigger haemolytic crises in SCD patients with glucose-6-phosphate dehydrogenase deficiency.

When an infection is suspected, proper chemotherapeutic treatment should be instituted immediately, especially in children. Proper nutrition should be encouraged and maintained. Tight clothing must be avoided because of danger of visceral organ constriction. Air flights above 3000 metres in non pressurised cabins should be avoided. The same is true for high mountain climbing and applies also to persons with sickle cell trait.

Prophylactic use of alkali to counteract acidosis may be justified in SCD patients with renal insufficiency or pulmonary infection. The last mentioned may also justify the use of oxygen, especially if the PaO2, falls below 70 mm Hg [22]. When alkalinisation is deemed necessary, sodium bicarbonate in oral doses of 2 to 4 g. per day can be given in two or three doses [23] or sodium citrate in 10% solution raised with water to 400 ml in doses of 60 ml orally every 4 hours for two days and thereafter every 6 hours until discharge [24]. Prophylactic blood transfusion in necessary before surgery under general anaesthesia.

Genetic counseling has a place in any discussion aiming at the prevention of SCD. However, dogmatism should be avoided and the choice should be left to the couples. Recent advances in prenatal diagnosis, for example with DNA recombinant method or Southern-blot hybridization [25-27] offer new possibilities of choice for advising the spouses. The risks of pregnancy especially in females with SS disease and sickle cell-ß^{o}-thalassaemia should be pointed out to the subjects. (See Trop GeogrMed 1983; 35:110 for reference)

Summary and Conclusion

In this lecture I have attempted to draw your attention to the sickle cell gene and its effects on the individual, the family and the community. The gene phenotypically manifests a disease which affects populations of tropical Africa and more so the great lakes region with a reported highest world incidence around the "Mountains of the Moon". The populations of the great lakes region all have one gene type known as the "Bantu haplotype" or the Kenya-haplotype, clinically manifesting as the severest type of SCD.

Whereas in the past it was considered a disease of children, we see an increasing number of young adults and adults with SCD who need education, jobs etc and need the society's attention. There is as yet no magical cure for the disease but with improved education and medical care an increasing number live fairly well into adulthood. Challenges lie into how we can still improve on the care of these patients who as time proceeds, will be seen in communities who were considered to be free from the gene. Challenges to the basic and clinical bench scientist abound in finding out among others an explanation to the love and hate affair between the HbS and malaria, and what malaria eradication may in the long run have on the reduction of the gene in heavily affected areas. Also still awaiting studies is the actual natural history of the disease i.e. HbSS disease in its indigenous environments, a study which can best be done in the great lakes region where the HbSS disease is the predominant form of the disease.

I thank you all for your attention.