# Sickle cell disease as a paradigm of immigration hematology: new challenges for hematologists in Europe

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While it is difficult to underestimate the implications of demographic change for world health,[1-3] for most hematologists such issues may seem far removed from everyday practice. Nevertheless, as genetic diseases are increasingly recognized as a major global health problem, many hematologists are already dealing with a new spectrum of disease which they need to be able to identify and manage. Arguably the disorders which best represent how hematologists have faced the challenges posed by *immigration* hematology are the hemoglobinopathies, particularly sickle cell disease. The implications are, however, much wider than the direct challenge of adapting services to meet our patients' needs. We also have to consider the needs of the vast numbers of patients in the less privileged countries where these disorders are endemic: it is sobering to realise, for example, that for every birth of a child with sickle cell disease in Europe, there are more than 90 in Africa! Increasing prevalence of previously rare disorders in Europe also requires changes to education and training, not only of hematologists, but of all physicians, medical students, paramedical staff and a wide variety of non-medical professional organizations indirectly involved in supporting patients with chronic disease. This article discusses the changing patterns of sickle cell disease prevalence and the implications for screening, service provision, education and training; as well as the opportunities for forging global networks to work towards improving access to medical care for all affected individuals.

## Epidemiology: the changing pattern of sickle cell disease worldwide

The hemoglobinopathies are the commonest, life-threatening, monogenic disorders in the world. Fairly recent estimates suggest that 7% of the world population are carriers and that 300,000–400,000 affected children are born every year.[4] The majority of these (approximately 250,000) have sickle cell disease. The highest frequency of sickle cell disease remains in tropical regions, particularly sub-Saharan Africa, India and the Middle East.[4] Migration of substantial populations from these high prevalence areas to low prevalence countries in Europe began more than 50 years ago but has dramatically increased with greater geographic mobility over the last 10-15 years[5-7] such that in some European countries sickle cell disease has now overtaken more familiar genetic disorders such as hemophilia and cystic fibrosis.[7,8] In most endemic countries there are no accurate figures of disease prevalence. A recent WHO report estimated that around 20 per 1,000 births in Nigeria were affected by sickle cell anemia, giving a total of 150,000 affected children born every year in Nigeria alone.[9] The carrier frequency ranges between 10% and 40% across equatorial Africa, decreasing to 1-2% on the north African coast and <1% in South Africa.[9] There is marked variation in carrier frequency, not only between countries (Table 1) but also between regions within individual countries, the Baamba tribe in western Uganda, for example, having a carrier frequency of 45%.[7,9,10] This variation means that accurate data are essential for characterizing the burden of disease and hence resource allocation, particularly in poorly-resourced countries. Some progress has already been made in thalassaemia through micromapping[1] and in sickle cell disease through the pioneering work of Graham Serjeant in Jamaica,[11] but there remains a huge task to complete. This work has implications not only in traditionally endemic countries, but also for the low prevalence countries to which many affected populations migrate.

Regional variation in the frequency of hemoglobin S (HbS) within the endemic countries of origin leads in turn, through the settling of immigrant populations in localized groups, to foci of high prevalence in their adopted countries (eg London, Birmingham, Paris, Brussels, Madrid and Copenhagen,[12-16] with consequent implications for screening and service provision.

There have been many national and local initiatives in non-endemic countries to obtain accurate, up-to-date measures of the changing prevalence of sickle cell disease,[5,7,12,13,15,17-20] although attempts to establish comprehensive national registries have so far largely failed, despite individual efforts, because of insufficient funding.[19,21] An alternative approach, which provides an essential starting point for planning purposes, is to estimate the carrier frequency using national population data including information about country of origin. In this way Modell and colleagues recently calculated the estimated proportions of residents and births in non-indigenous populations at risk of hemoglobin disorders (sickle cell disease and thalassemias) in Western, Northern and Southern Europe together with Bulgaria, Romania, Cyprus and Turkey.[7] These estimates showed that the highest proportion of the population carrying HbS was seen in Albania (3.0%), France (0.6%), Portugal (0.57%), Greece (0.53%), the

Netherlands (0.47%), England and Wales (0.47%), and Turkey (0.44%), this compares with only 0.01% in Scotland, 0.02% in Finland and 0.08% in Ireland. The highest number of carriers was seen in France, England/Wales and Turkey which were all estimated to have >200,000 HbS carriers and the total number of carriers in Europe was almost 1.5 million. Even in the lowest prevalence countries the increasing numbers of HbS carriers (eg >3,000 in Ireland in this study compared to only 60 known HbS carriers in 2001;[17]) is having, and will continue to have a major impact, particularly on pediatric and maternal services.

The high frequency of carriers, historically due to malaria-resistance, together with the improvement in life expectancy, even in poorer countries, means we can expect the prevalence of sickle cell disease to continue to increase for several generations, particularly in countries where migration is relatively recent and the migrant population is young. Recent work in Jamaica[22] also confirms predictions by Lucio Luzzatto more than 30 years ago that even if malaria was to be eradicated it would take 300 years for the frequency of HbS to reduce by 50%.[23] Further, as the study published in this month's journal from Telfer and colleagues in east London suggests, as services for affected children improve,[24] mortality in the first two decades may continue to fall such that the vast majority of children receiving optimal medical care will survive into adulthood with both direct implications for the prevalence of the disorder and possibly indirect ones (eg a reduction in uptake of prenatal diagnosis).

**Table 1.** Carrier frequencies for HbS (*modified from Weatherall & Clegg, 2001*).

| *Country* | *Carrier frequency (%)* |
|---|---|
| **Africa** | |
| Nigeria | 19-27 |
| The Gambia | 6-24 |
| Senegal | 5-15 |
| Liberia | 1-23 |
| Cote d'Ivoire | 3-22 |
| Mali | 7-29 |
| Ghana | 3-22 |
| Benin | 7-29 |
| Niger | 5-33 |
| Cameroon | 8-34 |
| Central African Republic | 1-21 |
| Gabon | 8 |
| Democratic Republic of Congo | 2-0 |
| Angola | 4-24 |
| Zambia | 6-27 |
| Uganda | 4-30 |
| United Republic of Tanzania | 10-38 |
| Kenya | 2-32 |
| Sierra Leone | 16-30 |
| **Eastern Mediterranean** | |
| Saudi Arabia | 1-29 |
| Iraq | 0-22 |
| **India** | |
| Madras | 20 |
| Andhra Republic Pradesh | 17 |
| Madhya Pradesh | 20 |
| Gujarat | 30 |
| Orissa | 25 |

### *Screening programmes for sickle cell disease*

Many countries have made the development of a comprehensive and reliable neonatal/antenatal screening programme a key strategy in their goal of delivering optimal health care to all patients with sickle cell disease,[25-28] *www.screening.nhs.uk/sickleandthal*. However, it is also clear that, despite the inherent practical, political and economic difficulties, progress is also being made in many endemic countries, including Nigeria, Ghana, Burkina Faso, Cameroon, Guinea-Bissau, Sudan, India and Brazil,[9,29-34] *www.ghanaweb.com; www.scinfo.org*. In Ghana, for example, >170,000 babies have been screened in Kumasi and Tikrom where Kwame Ohene-Frempong has been instrumental in establishing the first newborn screening programme for sickle cell disease in Africa (*www.ghanaweb.com*). This programme is groundbreaking, not only because it has led to the identification of >3,000 affected children, most of whom would have been unlikely to survive into adulthood, but also because of the careful work being done to link the laboratory results in practical, deliverable ways to the subsequent provision of clinical care by creating new, properly staffed, local clinics. Similar initiatives are clearly needed throughout sub-Saharan Africa and in other endemic areas. It is therefore encouraging that the Health Assembly of the WHO has recently urged Member States to mobilize resources for action on genomics and that the Assembly of the African Union now includes sickle cell anaemia in its list of public health priorities.[9] Progress is also likely through non-governmental organizations, such as the Federation des associations de lutte contre la drepanocytose en Afrique (FALDA), linking sickle cell centres in 13 West African countries, many of which have links with academic and fund-raising partners in Europe and the United States in order to support screening and clinical programmes not yet financed by national governments.

This principle, of matching screening to delivery of specialist follow on care for the affected individuals, is clearly also essential in well-resourced, non-endemic countries if the screening programme to ultimately deliver better care to patients. The recently established linked antenatal and newborn hemoglobinopathy screening programme in England and Wales is therefore closely linked with specialist fetal medicine and hematology services for carrier mothers and specialist paediatric services for children identified on the neonatal programme (*www.screening.nhs.uk/sickleandthal*). With this

screening programme and their matching clinical links in place, it should be possible to offer high quality care to all affected newborns throughout their childhood and beyond. In most endemic countries clinical networks will have to be initiated or extended from successful local pilot projects. In well-resourced countries, this will mainly be achieved through reorganization of current services and the formation of clinical care networks so that all patients have access to specialist care. This relies mainly on initiative and drive from within the profession together with the political will. Fortunately, in many countries this pattern of care should be possible to achieve with relatively little new expenditure since children can be cared for within existing paediatric services, although a modest expansion in specialist staff and equipment will be necessary in many centres and it is important that well organized and ambitious screening programmes are not hampered by the lack of the modest expenditure needed to deliver comprehensive care screening programmes. However, it is important to recognize that the resource implications of screening for sickle cell disease will also vary in individual countries. While specially trained nurses provide most of the information in the UK, in France genetic counselling is recommended to be carried out by geneticists- with almost 10,000 carriers of HbS/HbC identified every year, this places a particular burden on their service.

Selection of the most appropriate laboratory methods and strategies for screening have to be tailored to the epidemiological data gradually becoming available. Previous work has shown that *universal* screening of all pregnant women is cost-effective in areas of high prevalence (defined as a fetal prevalence of >1.5 affected babies/10,000 births).[35,36] This is the approach taken in England (*www.screening.nhs.uk/sickleandthal*) which offers universal screening in high prevalence parts of the country but targeted screening in lower prevalence regions. Targeted screening is used in many European countries, restricting tests to mothers and neonates whose parents originate from high prevalence countries.[25,37] In low prevalence areas various types of Family Origin Questionnaire have now been validated as an accurate tool for the identification of women and their partners at risk of being carriers for HbS or other abnormal sickle hemoglobins (eg HbC and HbD).[38,39]

The direct benefits of neonatal screening in sickle cell disease have been clearly documented, mainly though reduction in mortality through early introduction of penicillin prophylaxis.[40,41] The ethics of neonatal and antenatal screening are complex and only beginning to be addressed[25] but studies of the different issues in populations of varying origin, both in endemic countries and those to which they migrate, are an important aspect of being able to deliver screening goals and ongoing investigation of these ethical questions is essential. Recent data[42] and the paper by Paul Telfer in this issue[24] suggest that neonatal screening is likely also be associated with reduced morbidity. Telfer and colleagues followed a cohort of 252 children with sickle cell disease [(71%, 180 with homozygous sickle cell disease (HbSS)] identified by neonatal screening between 1983 and 2005. There were 2158 patient years of follow up and only 7 children were lost to follow up. Remarkably, only 2 children died, giving a mortality rate of 0.27/100 patient years while the rates of stroke and acute chest syndrome in HbSS were 0.3 and 17.1 per 100 patient years respectively. These rates are lower than a similar, but rather earlier cohort, of patients in the Dallas Cooperative Study where the mortality rate was 0.59 and the stroke-rate 0.85 per 100 patient years but which, in contrast to the London study, had a *lost to follow-up* rate of just over 16% (111 children)[43] supporting the value of neonatal screening when it is tightly linked to comprehensive hospital and community-provided care. Recent data from Belgium and France[44] are similar to the London data and also support this approach (*Ferster, unpublished observations)*. From a cohort of 115 children (84% HbSS) born between 1995 and 2006 followed up at a single centre in Brussels (497 patient years of follow up), 2 children died, 1 child developed a stroke and 17 children had one or more episodes of acute chest syndrome (*Aline Ferster, unpublished data*).

Although neonatal and antenatal screening targets two of the most critical groups, other target groups where screening can make an impact are young people at schools, colleges and universities and family planning or pre-marital clinics.[45] Together these screening programmes raise awareness of the disease and counselling patients found to be carriers must then be carried out by well trained individuals with specific knowledge of sickle cell disease. Hematologists also have a role in this. In some countries most of the counselling will be done by non-medical specialists, but in countries of very low prevalence it is likely that hematologists will play a direct role. In addition, in most countries, responsibility for the quality control of the laboratory methods used to ensure accurate diagnosis and interpretation of screening tests also lies with hematologists and in many countries this has been recognized by the formation of national or regional reference laboratories[46] usually linked to specialized clinical services.

### Hospital-based services for patients with sickle cell disease

The components needed to provide hospital-based comprehensive care for patients with sickle cell disease have been discussed and agreed by many regional and national groups in countries where the increasing prevalence of sickle cell disease has been recognized as a health priority.[47,48] These are summarised in Table 2. As mentioned above, in well-resourced coun-

tries many of these services will already be provided for patients without sickle cell disease. What is then required are detailed plans within each hospital to integrate these services to make them responsive to the specific needs of patients with sickle cell disease. The aim has to be to provide comprehensive, but also seemless and holistic, care to address all of the patients' needs rather than the fragmented care which is prevalent in hospitals which have not yet addressed the challenge of increasing numbers of sickle cell disease patients. Key to this is the clinical lead provided by the hematologist. In most centres they will be uniquely placed to integrate the clinical and laboratory service to cater for hemoglobinopathy patients, including blood transfusion.[49] As illustrated in the paper by Telfer *et al.*, a team approach involving nurse as well as medical specialists is a very successful model. In our experience too, this is the most effective way of providing holistic care for sickle cell disease patients who often face great difficulties accessing essential services both within and outside hospital.

Can this idealistic aim also be achieved in endemic countries where the clinical need is greatest? There are several impressive examples, particularly the pioneering work by groups in Jamaica, Ghana and the Republic of Benin, which show that, it can, although some very specialised services are clearly not yet possible.[41,50] The success of these services depends upon many factors, including clinical leadership from hematologists prepared to work in these local centres of need; financial support (usually from a combination of governmental and non-governmental organizations, including private companies); willingness to listen to and understand the local patterns of disease and care provision; and the establishment of networks[51] linking expertise in Europe and the United States with centres in Africa, India, South America and the Middle East.

### *Community-based services for patients with sickle cell disease*

In most European countries sickle cell disease has mainly been managed in hospital, with little involvement of teams in the community. This partly reflects the severity of the acute episodes and the need for access to parenteral analgesia, radiological investigations, blood transfusion and intensive care. However, it is also because community-based doctors and nurses in countries where sickle cell disease is newly prevalent, have little knowledge and experience of its management. In many countries, increasing prevalence of the disease and recognition of its chronic nature, is leading to changes in this hospital-focused pattern of service delivery,[52] *www.screening.nhs.uk/sickleandthal*. The aim is to allow patients more control over their disease, to spend more time at home rather than in hospital, to better fulfil their educational needs and aspirations by minimising time in hospital and to widen the scope of employment opportunities, as well as optimise family and social life. This approach should lead to further improvements in mortality, morbidity and quality of life for patients. In addition, the overall cost of treatment both in the short-term and long-term, should be lower. For the same reasons, community-based care is also a more appropriate model for endemic countries with very limited resources. The principal components of optimal community-based care are shown in Table 2. In countries where sickle cell disease has become the most prevalent severe genetic disorder, education about the disorder should be included within the curriculum of all medical and paramedical staff, as, for example, in the European Hematology Curriculum Passport which provides guidelines for the training of hematologists throughout Europe (*www.ehaweb.org*). In countries where the disease remains at a very low prevalence, it is likely that rolling programmes of education and training for staff in centres where most of the high risk population lives will be more effective. These should involve schools, universities and relevant local govern-

**Table 2. Comprehensive care for patients with sickle cell disease.**

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| **Emergency treatment** |
| Open access to a local hospital with audited, agreed guidelines for managing acute problems in sickle cell disease |
| Access to hospital in a clinical network with 24 hour available expert sickle cell guidance |
| Agreed protocols for transfer for seriously ill patients with sickle cell disease to centers of excellence, including access to intensive care and surgery. |
| **Hospital inpatient care** |
| Access to specialist sickle cell disease nurse |
| Designated hematologist/pediatric hematologist with knowledge of sickle cell disease |
| Access to high quality imaging- MRI, CT etc |
| Access to *pain team* with knowledge of sickle cell disease |
| Access to medical/pediatric specialist advice: neurology, orthopedics, gastroenterology, cardiology, ophthalmology, ENT, respiratory, surgery, anesthetics |
| Linked pediatric and adult service |
| Specialist transfusion and hematology laboratory support |
| Link to specialist obstetrics and fetal medicine |
| Links with dedicated stem cell transplant service |
| **Outpatient and community care** |
| Transcranial Doppler service |
| Access to specialist physicians for management of chronic conditions: renal, respiratory, cardiology, neurology, ophthalmology, ENT, surgery, endocrinology |
| Specialist sickle cell disease nurse |
| Clinical psychologist with specialist knowledge of sickle cell disease |
| Genetic counselling |
| Social worker with specialist knowledge of sickle cell disease |
| Informed community doctor (General Practioner) |
| Patient support groups and charities |

ment departments, as well as clinical teams. These initiatives are important not only in providing better care for patients with sickle cell disease, but also in disease prevention though early carrier identification prior to pregnancy and can have additional benefits, if carefully harnessed, such as increasing the number of blood donors in high risk populations to better address the blood transfusion needs of these patients.[53]

### Research networks in sickle cell disease and their role in improving patient care worldwide

Fortunately, the increasing numbers of patients living with sickle cell disease, has been accompanied by a marked increase in medical and academic interest in the disease and to very significant progress in our understanding both of the pathogenesis of acute and chronic disease manifestations and of the genetic and biological basis for the enormous variability in phenotypic expression of the disease.[11,51,54,55] Much of this work is facilitated by very careful observations of the natural history of disease and by the formation of clinical research networks within and between countries.[56-58] Nevertheless, there remains an urgent need to extend these networks more effectively to include the large number of African countries where, so far, there is not only limited detailed prevalence data as discussed above, but also very little information about the clinical features of the disease.[51,59] Differences in prevalence of the common infective organisms in patients with sickle cell disease between African and European countries, for example, are crucial to identify since this will dictate the effectiveness of prophylactic measures. Penicillin prophylaxis has played a major role in reducing mortality in developed countries[60] and it is important to find out whether it will be similarly beneficial in African countries where several groups have found that Streptococcus pneumoniae is also a major cause of morbidity and mortality[61,62] whereas others report that it is less common.[63] The growth of research collaborations in sickle cell disease between developing countries and well resourced countries[31,32,61-63] has recently been highlighted as an important tool for improving clinical and diagnostic facilities in developing countries as well as advancing our knowledge of disease pathogenesis.[51]

### Future challenges and priorities in sickle cell disease worldwide: the role of the hematologist

Despite progress both in basic and clinical research and in the establishment of care networks and clinical and laboratory guidelines in well-resourced countries, there remains a huge task to provide equal access to high quality care for all patients in all countries. This task is critically dependent on hematologists. The priorities are listed in Table 3. First, it is essential to continue to raise awareness about sickle cell disease at local, regional and government level in countries where sickling disorders are common or increasing and in international health agencies such as the WHO. Such iniatives could also be useful for driving forward targeted international collaborative efforts with a specific goal, such as widening access to vaccination programmes by reducing vaccine costs. Second, accurate data must be collected about current and predicted carrier frequency and disease prevalence in order to calculate the burden of disease and design services to take account of future need.

**Table 3.** Future challenges and priorities in sickle cell disease.

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|---|
| Raising awareness of sickle cell disease with local, national and international health agencies |
| Accurate data collection: current and predicted carrier frequency and disease prevalence |
| Reliable, cost-effective screening programs to identify carriers and affected children |
| Establishment of clinical networks adapted to local needs, resources and patterns of disease matched to central reference laboratories |
| Collection and analysis of clinical data about natural history and treatment to enhance undertsanding of pathogenesis and audit clinical care |
| Research collaborations between developing countries and well resourced countries to advance knowledge and improve access to optimal care worldwide |

The need for actual disease prevalence is particularly important in order to take account of families with affected children who move between countries as these cases will not be captured by neonatal or antenatal screening programmes and can account for a significant proportion of the disease burden in many countries. In our experience in Paris and London, for example, around 10% of parents of children under our care have moved to Europe because of their desire to give their children better care, including bone marrow transplantation.

Third, reliable, cost-effective screening programmes should be established to identify carriers and affected children at an early stage to reduce the frequency of unexpected births and early deaths. It should be acknowledged that while antenatal screening has had a major impact on the prevalence of thalassaemia in many countries,[7] the impact of antenatal screening in sickle cell disease has hitherto been modest[64] and the principal benefits may lie more in raising awareness and avoidance of subsequent pregnancies rather than reducing the number of affected children via prenatal diagnosis. Fourth, managed clinical networks adapted to local needs, resources and patterns of disease must be put in place to provide optimal care for newly identified and existing patients.

These must be matched with a reliable hematological and molecular diagnostic service networked in to central reference laboratories. Fifth, clinical data about the natural history of the disease, the treatment used and the treatment outcome should be collected and audited, perhaps via specialized registries. Finally, as discussed above, research collaborations between developing countries and well resourced countries should provide mutually beneficial links for advancing our knowledge of disease pathogenesis as well as for improved patient care.[51]

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