Sickle cell disease from Africa to Belgium, from neonatal screening to clinical management

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ABSTRACT • *Aim.* To describe the severity of sickle cell disease (SCD) in newborns in Belgium and evaluate the impact of neonatal screening (NS) on clinical outcome. *Methods.* Universal NS of umbilical cord blood for hemoglobinopathy was progressively deployed in Brussels and Liège starting in 1994. No particular population was targeted. Samples were analyzed initially using the isoelectric focusing technique and since 2008 the capillary electrophoresis technique. If a hemoglobin variant was suspected, further analysis was carried out using high performance liquid chromatography. Children presenting major hemoglobinopathy, especially SCD, were referred to a specialized centre for comprehensive management. Preventive measures included antipneumococcal prophylaxis immunization / antibiotic therapy, parental training to recognize severe anemia and splenic sequestration, and transcranial ultrasound recording for early detection of intracranial stenosis. A database was set up in Belgium to collect clinical and laboratory data including parental phenotype, diagnostic technique (neonatal screening or not), major clinical events (episodes of dactylitis, acute chest syndrome, severe anemia, infection, etc), number and duration of required hospitalizations, and treatment used. *Results.* Screening of 222352 newborns in maternity units in Brussels led to diagnosis of SCD in 145 patients, Adequate data for analysis of clinical outcome was available for 96 of these children born before 2007. Median age in the study group was 4.2 years and the total duration of follow-up was 510 years. Most cases occurred in families from the Democratic Republic of Congo. (64/96 patients; 66.7%) and involved homozygous hemoglobin S disease (80/96 patients; 83.3%). Twenty-seven percent of patients (26/96) presented no severe clinical events during the study (17 SS, median age 2,1 years (0-13.1 years). Conversely 33% presented an episode of dactylitis and 47.9% (46/96) presented recurrent vasoocclusive crises. Severe anemia was observed in 39.6% (38/96) of cases. Six patients (6.3%) developed septicemia despite prophylactic antibiotic therapy and anti-pneumococcal immunization using heptavalent conjugate vaccine and polysaccharide vaccine, No penicillin-resistant strains were observed. The incidence of stroke was 2.1% (3/96). Two patients presenting homozygous hemoglobin S disease died due to septicemia due to non-compliance with antibiotic therapy in one case and severe anemia in one case. All episodes of septicemia and both deaths occurred at the beginning of the NS program. Hydroxyurea therapy was used in 30 patients (31.2%) including 7 in whom transcranial Doppler depicted blood flow abnormalities and 8 in whom allogeneic bone marrow transplantation was performed. *Conclusions.* Sickle cell disease is still associated with high morbidity and mortality but clinical care has improved and no death has occurred in the last 10 years. NS is an effective tool for early detection and management of SCD. Neonates with SCD diagnosed by NS in Belgium presented severe manifestations, but clinical outcomes were improved by comprehensive management.

KEY WORDS • Sickle Cell Disease. Screening and Management.

DRÉPANOCYTOSE DE L'AFRIQUE À LA BELGIQUE, DU DÉPISTAGE NÉONATAL À LA PRISE EN CHARGE CLINIQUE

RÉSUMÉ • *But.* Cette étude permet de décrire la sévérité des syndromes drépanocytaires chez les patients vivants en Belgique ainsi que de mesurer l'impact du dépistage néonatal sur cette sévérité. *Méthodes.* Le dépistage néonatal est réalisé au sang du cordon ombilical et n'est pas ciblé sur une population particulière. Les échantillons sont analysés par une technique de focalisation isoélectrique, et depuis 2008 par une technique d'électrophorèse capillaire. Si un variant de l'hémoglobine est suspecté, une seconde technique de chromatographie liquide à haute performance est utilisée. Les enfants atteints d'une hémoglobinopathie majeure, et plus particulièrement d'un syndrome drépanocytaire sont référés à un centre spécialisé pour une prise en charge globale et adaptée. Parmi les actions préventives, on peut citer la prophylaxie antipneumococcique par vaccination et antibiothérapie, la formation des parents à la reconnaissance d'une anémie sévère et d'une séquestration splénique, et la prévention des accidents cérébrovasculaires par la réalisation d'un doppler transcrânien. En Belgique, une base de données cliniques et biologiques a été créée. Les données collectées incluent entre autres le phénotype des patients, le mode de diagnostic (via le dépistage néonatal ou non), les événements cliniques critiques (les épisodes de dactylite, de syndrome thoracique aigu, d'anémie sévère, d'infection, etc), le nombre et la durée de chaque hospitalisation ainsi que les traitements instaurés. *Résultats.* Parmi les 222 352 nouveau-nés dépistés, 145 ont été diagnostiqués comme drépanocytaires. Ils sont suivis dans trois centres de référence. Un dossier clinique complet et suffisant a été obtenu pour 96 d'entre eux. Leur médiane d'âge est de 4,2 ans et ce groupe représente 510 années de suivi clinique. Ils sont majoritairement originaires de la République Démocratique du Congo (66,7%) et homozygotes pour l'hémoglobine S (83,3%). Si 27% (26/96) des patients n'ont pas encore présenté d'évènements cliniques sévères (17 SS, âge médian 2,1 ans (0-13,1 ans)), un tiers des patients ont présenté un épisode de dactylite et 47,9% (46/96) des crises vaso-occlusives récurrentes. L'anémie sévère a été observée dans 39,6% (38/96) des cas. Malgré l'antibiothérapie prophylactique et la vaccination antipneumococcique (vaccin conjugué heptavalent, et vaccin polysaccharidique), six patients (6,.3%) ont présenté une septicémie ; aucun germe n'était résistant à une pénicillothérapie. L'incidence d'accident cérébrovasculaire est de 2,1% (2/96). Deux décès de patients homozygotes pour l'hémoglobine S sont à déplorer ; l'un d'une septicémie consécutive à une non adhérence à l'antibiothérapie et l'autre suite à une anémie sévère. Les épisodes de septicémie et les deux décès ont été observés au cours des premières années d'installation du programme de dépistage néonatal. Trente (31,2%) patients ont été traités par hydroxyurée, dont sept pour des anomalies du flux sanguin détectées au doppler transcrânien, et huit ont bénéficié d'une greffe de moelle allogénique. *Conclusion.* la drépanocytose reste une maladie à haute prévalence de morbidité et de mortalité. Le dépistage néonatal systématique est un outil efficace dans la détection de la maladie et pour l'instauration d'un programme global de soins. En Belgique, les nouveau-nés diagnostiqués comme drépanocytaires présentent un tableau clinique particulièrement sévère, mais celui-ci est nettement amélioré grâce à un programme global de prise en charge.

MOTS-CLÉS • Database. Neonatal screening. Sickle cell disease.

Sickle cell disease (SCD) is an autosomal recessive genetic disorder of hemoglobin due to a mutation in the β globin gene. It is characterized by abnormal, rigid, sickle-shaped red blood cells with reduced life span and membrane flexibility that leads to various clinical complications and shortens life expectancy (1, 2). SCD occurs throughout the world, with highest incidence in sub-Saharan Africa. As a result of migration, SCD is the most common monogenic

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disease in Northern Europe. Although there is now a better understanding of the physiopathology of SCD, clinical outcome remains uncertain, particularly in developing countries (3). A number of potentially severe complications of SCD can develop early in life. Neonatal screening (NS) enables early diagnosis and prompt treatment, thereby improving overall mortality rates (4). The purpose of this study conducted in pediatric centers in Belgium was to describe the severity of SCD in newborns and evaluate the impact of neonatal screening (NS) on clinical outcome.

Material and methods

Universal NS was progressively implemented in Brussels starting within a few maternities in 1994 and extending to all maternities in 2000. Since 2001, universal NS has also been started in Liège. All neonates born at all maternity facilities in Brussels and two in Liège have been undergoing NS since 2003.

Umbilical cord blood samples were screened initially using an isoelectric focusing technique (Perkin Elmer Life Sciences, Zaventem, Belgium) and since 2008 using a capillary electrophoresis technique (Sebia Benelux, Vilvoorde, Belgium). If a hemoglobin variant was detected, further analysis was performed using high performance liquid chromatography (BioRad, Hercules, California, USA). Children presenting major hemoglobinopathy were referred to a specialized center for clinical management. All children with SCD received antibiotic prophylaxis until at least up five years of age and vaccination against Streptococcus pneumonia (including conjugate vaccines since 2004). Starting in 1999, one facility began to use transcranial Doppler (TCD) ultrasonography for follow up of SCD patients and this technique is now being extended to all facilities.

Data obtained for all the patients who underwent NS in this study were included in a database created to collect clinical and laboratory findings and monitor outcome in SCD patients in Belgium.. Collected data included parental origin and hemoglobin phenotype, diagnostic technique (neonatal screening or not), laboratory and radiological findings, major clinical events (e.g. episodes of dactylitis, acute chest syndrome, vaso-occlusive crisis, splenic sequestration, stroke, avascular necrosis, and major infection), number and duration of required hospitalizations, and treatment used.

To ensure patient confidentiality, data were processed in compliance with legal requirements and privacy guidelines. Informed consent was obtained from all patients (or their parents/legal guardians). Data collection and registry were approved by each local ethics committee in accordance with the principles of the Declaration of Helsinki.

Results

Patients

Between 1994 and 2009, NS of umbilical cord blood for hemoglobinopathy was performed on 222352 newborns in Brussels maternity units and led to diagnosis of SCD in 145. All major hemoglobinopathies were confirmed by further analysis and follow-up was provided to all but three affected infants who failed to attend the first medical consultation despite all our best efforts (5). To allow meaningful assessment of clinical outcomes, analysis was focused on data from the 99 patients born before 2007.

A full clinical history was obtained for 96 of these 99 patients including 53 females and 43 males with a median age of 4.2 years at last follow-up (range: 0-17 years). Cumulative follow-up duration was 510 years. Two patients were lost to follow up, two died, and one emigrated to U.S.A. Eighty-four had the most severe SCD phenotypes (SS and Sβ0) that accounted for 87.5% of cases. Other phenotypes are listed in table 1. Ninety-one patients were followed regularly in three dedicated pediatric centers, two thirds in one pediatric hospital. Most patients originate from central African countries (70.8% [68/96]), particularly the Democratic Republic of Congo (66.7% [64/96]) (figure 1).

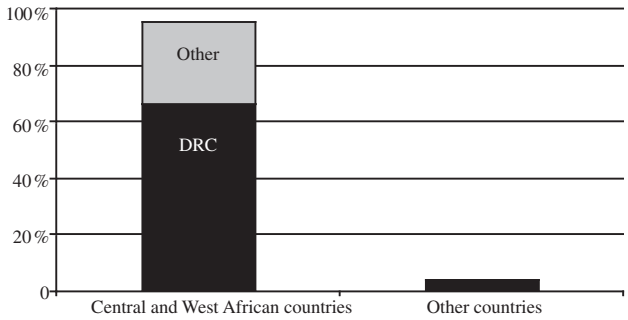

Figure 1. Distribution of the patients' origin of the Belgian Neonatal Screening Database.
DRC = Democratic Republic of Congo

Clinical events

Seventy-three percent of the patients (70/96) had severe clinical events (Table 2). The remaining 26 patients (26/96) remained symptom-free (17 SS, 3 Sβ0, and 6 SC), at a median age of 2.1 years (range, 0-13.1 years). One third of patients in the symptomatic group presented dactylitis and nearly half had recurrent vaso-occlusive crises (VOC). More than one third of symptomatic patients (38/96) presented one or more episodes of acute anemia (Hb < 60 g/L). The rate of septicemia was relatively high (6.3%) despite early systematic prophylactic treatment. The most common pathogen was Streptococcus pneumoniae,. Two cases of Streptococcus pneumoniae septicemia occurred in the first six years of the NS program before optimization of comprehensive management. All strains of Streptococcus pneumoniae implicated in septicemia were sensitive

Table 1. Phenotypes of the 96 SCD Patients.

Phenotypes	Patients % (n)	Females/Males
SS	83,3 (80)	44/36
SC	10,4 (10)	6/4
Sβ0	4,2 (4)	2/2
Sβ+	2,1 (2)	1/1

Table 2. SCD-Related Events of the 96 patients reported in the Belgian Neonatal Screening Database.

SCD-Related Events	Patients % (n) N=96	Phenotype SS/Sβ°/SC
Dactilytis	33,3 (32)	31/1/0
Acute Chest Syndrome	15,6 (15)	15/0/0
Recurrent Vaso-occlusive Crisis	47,9 (46)	43/1/2
Anaemia ≤ 60 g/L	39,6 (38)	36/1/1
Septicaemia	6,3 (6)	6/0/0
Splenic Sequestration	8,3 (8)	8/0/0
Stroke/Transient Ischaemic Attack	2,1 (2)	2/0/0
Osteonecrosis	2,1 (2)	2/0/0
Osteomyelitis	1,0 (1)	1/0/0

Table 3. Episode of septicaemia in SCD patients of the Neonatal Screening Database

Patient	Age at event	Pmeumococcal vaccination and prophylaxis	Pathogen	Sensitivity	Outcome
1 (SS)	12 months	Yes*	*Streptococcus pneumoniae*	Pen S	Recovery
2 (SS)	13 months	Yes*	*Streptococcus pneumoniae*	Pen S	Recovery
3 (SS)	26 months	Yes*	*Streptococcus pneumoniae*	Pen S	Death
4 (SS)	2 years, 7 months	Yes	*Streptococcus pneumoniae*	Pen S	Recovery
5 (SS)	4 years, 4 months	Yes	*Streptococcus pneumoniae*	Pen S	Recovery
6 (SS)	6 years, 2 months	Yes*	*Stenotrophomonas maltophilia*	Pen R	Recovery

Key: Pen S = Penicillin Sensitive; Pen R = Penicillin Resistant

*: before the conjugate vaccine era

to penicillin. One patient (2 years old) developed overt stroke and another had seizures with abnormal TCD velocities but normal magnetic resonance angiography (MRA). Stroke rate accounted for 0.39% patient-years.

Thirty children received hydroxyurea (HU) therapy mainly for recurrent VOC or acute chest syndrome.

Indications for HU therapy were ≥ 2 VOC requiring hospitalization, one episode of acute chest syndrome, more than one episode of splenic sequestration, recurrent transfusion for severe anemia, and sometimes recurrent dactylitis (6). In 7 of the 30 patients treated using HU, the indication was abnormal blood flow velocity detected on TCD. Only one patient was under chronic transfusion for overt stroke. Patients responded well to intensified treatment options.

Hematopoietic stem cell transplantation (HSCT) was performed in 8 including 5 with severe clinical disease at a median age of 9.6 years. As previously described (data not shown), the number of VOC crises decreased under HU therapy. All patients who underwent HSCT were cured.

Mortality was 2.1% (2/96). One death occurred during early childhood clearly due to non -compliance with antibiotic prophylaxis. The other death was attributed to severe anemia. Both deaths occurred before 2000 and involved patients homozygous for Hb S.

Discussion

This prospective cohort study of SCD patients screened at birth in pediatric centers in Belgium confirmed the high multisystem morbidity observed elsewhere (6-11). Mortality in our study was high considering the relatively low median age of the cohort. Nevertheless it must be noted that all deaths occurred immediately after the start of NS program before optimization of comprehensive management, especially regarding parental education and psychosocial support. No death has occurred in the screened cohort in the last 10 years. Another notable finding was the high prevalence of SCD, thus confirming it as the most common genetic disorder screened in the world. It exceeds cystic fibrosis with an estimated frequency of 1/2500 live Caucasian births in western countries (12) One of the main characteristics of our cohort was the predominance of patients from central African countries (71%), particularly the Democratic Republic of Congo (DRC). There was the high incidence (87.5%) of severe sickle cell disorders, i.e.,. Hb SS and Hb Sβ0. This incidence is much greater than in previous studies describing NS in France, UK, and USA.

With regard to SCD-related complications, it should be underlined that 50% of our patients presented recurrent VOC despite their young age. This rate is similar to those reported in the literature. The incidence of dactylitis (33.3%) was also similar to those in previously reports. Conversely, the incidences of acute chest syndrome and stroke were relatively lower than reported elsewhere, i.e., 15.6% and 2.1% respectively. This was probably due to the young age of our cohort and to the use of HU therapy in one third of the patients and of screening using TCD. Another complication of SCD was severe anemic episodes requiring transfusion. The suspected relationship between this complication and glucose-6-phosphate deficiency remains unclear since detection was not routinely performed in some centers. The septicemia rate observed in this study was slightly lower than those reported in previous studies before routine

use of antibiotic prophylaxis and conjugate vaccine (7, 10). The limited impact of early combined use of prophylactic penicillin and immunization with both heptavalent-conjugate pneumococcal (PCV-7) and 23-valent pneumococcal polysaccharide (PPV-23) vaccines was still worrying. Nevertheless, the death rate due to bacterial infection was low. The only patient who died from Streptococcus pneumoniae infection was diagnosed soon after the start of the NS pro-gram before the availability of conjugate vaccine. Conjugate vaccine has been clearly shown to provide good protection against most strains present in Western countries (13) but its usefulness in sub-Saharan countries is unclear. The finding that all Streptococcus pneumoniae strains in our SCD cohort were penicillin-sensitive is interesting since it indicates that long-term antibiotic prophylaxis does not jeopardize the response to antibiotics.

In our cohort, HU therapy was administered to almost one-third of patients and showed clear sustained clinical efficacy. The clinical safety and efficacy of HU therapy has been documented for over 25 years. Various studies in both adults and pediatric cohorts have confirmed the value of HU therapy in preventing vaso-occlusive events (6, 14, 15, 16, 17, 18). Studies also indicate that HU may provide protection against primary and secondary stroke, spleen dysfunction, and proteinuria (19, 20). At one hospital participating in this study, HU was used for primary stroke prevention after detection of abnormal cerebral velocity by transcranial Doppler. This preventive approach was implemented because of the high rate of severe alloimmunization related to the lack of blood donors of African origin (19) and previous poor transfusion policy. Further prospective evaluation of this policy will be needed. In this regard, preliminary findings of the randomized SWiTCH study comparing HU plus phlebotomy to transfusion and chelation in SCD patients at risk for stroke associated with iron overload will soon be available (6).

HSCT was used as an alternative treatment in severe cases of SCD. Due to the complexity and potential risks of the procedure, however, indications were limited to patients who had a sibling with a human leukocyte antigen. In our cohort, eight patients underwent HSCT including 5 with severe SCD-related complications (20, 21). Bone marrow transplantation is the only treatment that can achieve complete cure.

Conclusion

The results of this study indicate that universal NS program was a feasible and effective method for detection of SCD. No case of major hemoglobinopathy was overlooked. Children diagnosed with SCD-affected benefited from comprehensive expert medical care in dedicated centers. Care included education, prevention, emergency treatment, and specific out-patient and in-patient care.

Regarding severity of SCD in Belgium, our results showed that morbidity was high but that mortality was low. These findings underline the need for constant surveillance as well as the importance of maintaining the universal NS program. Early detection allows prevention of early death and complications by undertaking prompt management including administration of prophylactic antibiotic treatment and immunization with PCV-7 and PPV-23. Study data also underline the importance of parental education and comprehensive SCD care in improving clinical outcome.

In the future the clinical database will be an important tool for improving clinical management of SCD patients, identifying potential risk factors, and tailoring treatments. The database will also constitute a basis for prospective studies to validate criteria of disease severity and develop guidelines for optimal treatment.

It would be interesting to create a partnership with working groups in developing countries. Our registry could be adapted to the natural history and diversity of clinical events observed in these countries. This cooperation would provide an opportunity to improve and target required clinical services.

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