Newborn screening for sickle cell disease: A 1988–2003 Quebec experience

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BACKGROUND: Sickle cell disease (SCD) is associated with significant mortality and morbidity that can be decreased by neonatal diagnosis. Although 44 American states have implemented such programs, there are no provincially funded universal or targeted newborn screening programs for SCD in Canada.

OBJECTIVE: To report a critical appraisal of a hospital-based neonatal screening program targeting at-risk infants over a 15-year period.

METHODS: The cord blood of infants born at Sainte-Justine University Health Centre (Sainte-Justine UHC, Montreal, Quebec) whose mother or father was black was collected at birth and analyzed for the presence of hemoglobin (Hb) S by liquid chromatography or isoelectric focusing. Samples with positive results underwent confirmatory testing.

RESULTS: A total of 9619 infants were screened: 8142 (84.6%) had a normal phenotype, 1012 (10.5%) had sickle cell trait and 386 (4.0%) had HbC trait. Seventy-two infants were diagnosed with SCD: 37 (0.4%) were classified as HbSS or HbS-beta-thalassemia and 35 (0.4%) had HbSC disease. Of these 72 infants, 67 (93.1%) were immediately enrolled in a multidisciplinary SCD follow-up clinic. The five remaining children not initially enrolled were later referred to the clinic. A chart study revealed that six patients with SCD born at Sainte-Justine UHC were not identified by neonatal screening.

CONCLUSIONS: The screening program was clinically effective because it identified 92.3% of at-risk patients born at Sainte-Justine UHC. These infants received appropriate medical care before 10 weeks of age as opposed to a median of 12 months for infants not identified by the screening program. It is proposed that either a targeted or a universal neonatal screening for SCD should be available in Canada.

Key Words: *Neonatal screening; Sickle cell disease*

Le dépistage néonatal de l'anémie falciforme au Québec de 1988 à 2003

HISTORIQUE : L'anémie falciforme est associée à des taux de mortalité et de morbidité élevés qui peuvent être réduits par le dépistage néonatal. Bien que 44 États américains aient implanté des programmes de dépistage, aucune province canadienne ne finance actuellement des programmes de dépistage universel ou ciblé de l'anémie falciforme chez les nouveau-nés.

OBJECTIF : Procéder à l'évaluation critique d'un programme de dépistage néonatal de l'anémie falciforme en milieu hospitalier ciblant les nourrissons à risque, et ce, sur une période de 15 ans.

MÉTHODOLOGIE : Le sang du cordon ombilical des nourrissons dont la mère ou le père était de race noire a été prélevé à la naissance et analysé en vue de déceler la présence d'hémoglobine (Hb) S par chromatographie liquide ou par électrofocalisation. Les échantillons positifs ont fait l'objet d'une épreuve de confirmation.

RÉSULTATS : Au total, 9 619 nourrissons ont été dépistés : 8 142 (84,6 %) avaient un phénotype normal, 1 012 (10,5 %) avaient un trait HbS et 386 (4,0 %) avaient un trait HbC. On a diagnostiqué l'anémie falciforme chez 72 nouveau-nés : 37 (0,4 %) avaient une anémie falciforme de type HbSS ou HbSβ-thalassémie et 35 (0,4 %) avaient une anémie falciforme de type HbSC. De ces 72 nourrissons, 67 (93,1 %) ont été aiguillés immédiatement vers la clinique multidisciplinaire d'anémie falciforme. Les cinq nouveau-nés n'ayant pas été dirigés initialement à la clinique l'ont été ultérieurement. Une étude de dossiers a révélé que six enfants nés au CHU Sainte-Justine (Montréal, Québec) n'avaient pas été repérés par le dépistage néonatal.

CONCLUSIONS : Le programme de dépistage a permis de repérer 92,3 % des nourrissons à risque nés au CHU Sainte-Justine, ce qui démontre son utilité clinique. Ces nouveau-nés ont reçu des soins médicaux adéquats avant l'âge de dix semaines comparativement à une médiane de 12 mois chez les nourrissons n'ayant pas été repérés par le programme de dépistage. Les auteurs suggèrent qu'un programme de dépistage universel ou ciblé soit offert au Canada.

Sickle cell disease (SCD) consists of a group of autosomal, recessively inherited hemoglobin (Hb) disorders characterized by Hb polymerization on deoxygenation, which in turn leads to erythrocyte injury (1). The most common of these disorders, sickle cell anemia, arises from a homozygous state for a point mutation affecting the beta-chain gene of adult Hb (HbA), which results in the replacement of glutamic acid by valine at position 6 of the beta-chain. Other sickling diseases, of varying clinical severity, occur when the sickling gene coding for Hb S (HbS), inherited from one parent, is associated with either a beta-thalassemia gene, resulting in a condition known as HbS-beta-thalassemia, or the HbC gene, resulting in HbSC disease (2). HbC results from a point mutation in the beta-chain gene of HbA, which results in the replacement of glutamic acid by lysine at position 6 of the beta-chain. SCD is particularly prevalent in individuals of African ancestry, but it is also present in populations of Mediterranean, Middle Eastern, Indian and Hispanic descent (3,4). In the United States, the birth prevalence of SCD in the African-American population is estimated to be one in 400 (5). To our knowledge, there are no reports on the nationwide birth

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prevalence rate for SCD in Canada in either the general population or the black population. Ali and Lafferty (6) reported the results of the Regional Hemoglobinopathy Laboratory at St Joseph's Hospital (Hamilton, Ontario) over a 20-year period. However, strict comparisons cannot be made with the present study because testing was performed following referrals and not as part of a screening program.

Although newborns and very young infants are usually asymptomatic due to the presence of fetal Hb (HbF), SCD may be associated with significant mortality and morbidity early in life, and the first clinical manifestation of the disease can be life-threatening (7-11). Common clinical manifestations of SCD include splenic sequestration; sepsis due to infections with encapsulated bacteria, particularly *Streptococcus pneumoniae* (patients are prone to sepsis because of functional asplenia caused by splenic infarcts); episodes of severe pain; acute chest syndrome (acute onset of respiratory symptoms and signs with pulmonary infiltrates that may or may not have an infectious etiology); stroke; and multiple-organ dysfunction (7-14). Splenic sequestration and pneumococcal sepsis are the commonest causes of early mortality. Early studies reported a mortality rate of 20% in children with sickle cell anemia during the first decade of life (15). In 1986, Gaston et al (16) clearly demonstrated an 84% decrease in the incidence of *S pneumoniae* infections in infants with SCD receiving oral penicillin prophylaxis when compared with those who had not received this prophylactic treatment. Furthermore, there were no deaths in the penicillin-treated group compared with three deaths in the placebo group (16). In 1988, Vichinsky et al (17) demonstrated that the overall mortality rate for American patients with sickle cell anemia diagnosed in the neonatal period was 1.8% compared with 8% for children diagnosed after three months of age. These and later studies have clearly established that morbidity and mortality can be significantly reduced by universal newborn SCD screening programs combined with comprehensive medical follow-up in a multidisciplinary program that includes parental education (18-21).

Following publication of the study by Gaston et al (16), the National Institutes of Health in the United States convened a Consensus Development Conference to address issues related to newborn screening for SCD. The panel's conclusions were as follows:

> "… the panel recommends universal screening of all newborns for hemoglobinopathies. Programs that screen only specific high risk segments of a population tend to miss individuals who are inaccurately registered and to encourage nonscreening because of provider complacency. This panel believes that the health risks to children with sickle cell disease are so great that major efforts should be made to identify every affected child. For those states with very few at-risk members, targeted screening might be considered …" (5).

This recommendation resulted in 44 American states and the District of Columbia, as well as Puerto Rico and the Virgin Islands, having universal newborn screening programs for SCD and the remaining six states having screening available by request (as of March 2002) (22). To our knowledge, no newborn screening program for SCD, other than the one described in the present report, exists in Canada. A pilot study (23) was carried out in one hospital in Montreal, Quebec, in the early 1990s, but has been discontinued for several years. In January 1988, the Sainte-Justine University Health Centre (Sainte-Justine UHC, Montreal), a tertiary care mother-child centre, realizing the need for early diagnosis of SCD in a demographically changing population, instituted a targeted newborn screening program for SCD. A retrospective critical appraisal of this program from its inception until June 30, 2003, is reported.

METHODS

In January 1988, a program of neonatal screening for SCD targeting all infants born at Sainte-Justine UHC whose mother or father was black was begun. Identification of black parentage was made by the ward staff, especially nurses. Screening was performed on cord blood collected by direct venipuncture of the umbilical vein at the time of delivery.

The analytical methodology followed the technology developments that occurred and were available at Sainte-Justine UHC over the past 15 years. From January 1988 to March 1994, samples were analyzed by fast-performance liquid chromatography; from March 1994 to November 1996, samples were analyzed by isoelectric focusing; and from November 1996 on, high-performance liquid chromatography was used. All of these methods have been shown to be very accurate for the diagnosis of sickling hemoglobinopathies in the newborn (3,17,23-26). For example, high-performance liquid chromatography has a 0.5% detection limit for HbS, which is much higher than the 7% HbS a term newborn with sickle cell trait would have (26). A presumptive diagnosis of SCD was made if one of the three following Hb combination patterns was obtained: FS (presence of HbF and HbS, and absence of HbA), indicating sickle cell anemia or HbS-beta^0-thalassemia; FSC (presence of HbF, HbS and HbC, and absence of HbA), corresponding to a compound heterozygote HbSC; or FSA (presence of HbF, HbS and HbA, with the amount of HbA being less than that of HbS), indicating HbS-beta$^+$-thalassemia. Sickle cell trait was diagnosed if the pattern was FAS (ie, presence of HbF, HbA and HbS, with HbA and HbS in approximately equal proportions or a quantity of HbA greater than that of HbS). HbC trait was diagnosed if the pattern was FAC (ie, presence of HbF, HbA and HbC). HbC disease or HbC-beta^0-thalassemia was diagnosed if the pattern was FC (presence of HbF and HbC, and absence of HbA). On occasion, additional studies (including parental studies) were necessary to distinguish FSA and FAS results.

Newborns with a presumptive diagnosis of SCD were evaluated at Sainte-Justine UHC's multidisciplinary SCD clinic within 10 weeks of birth. The multidisciplinary team

TABLE 1
Newborn screening results from January 1988 to June 2003

Hemoglobin pattern	Interpretation	Number	Percentage*
FA	Normal	8142	84.6
FAS	Sickle cell trait	1012	10.5
FAC	HbC trait	386	4.0
FS or FSA	Sickle cell anemia or HbS-beta^0-thalassemia or HbS-beta$^+$-thalassemia	37	0.4
FSC	HbSC disease	35	0.4
FC	HbCC or HbC-beta^0-thalassemia	7	0.07
	Total	9619	100

**Percentages do not add up to 100% due to rounding. FA Presence of fetal hemoglobin (HbF) and adult Hb (HbA); FAC Presence of HbF, HbA and HbC; FAS Presence of HbF, HbA and HbS, with HbA and HbS in approximately equal proportions or a quantity of HbA greater than that of HbS; FC Presence of HbF and HbC, and absence of HbA; FS Presence of HbF and HbS, and absence of HbA; FSA Presence of HbF, HbS and HbA, with the amount of HbA being less than that of HbS; FSC Presence of HbF, HbS and HbC, and absence of HbA; HbSC Sickle-HbC*

TABLE 2
Neonatal screening follow-up

	Number	Percentage
SCD patients born at Sainte-Justine UHC*	78	100
SCD patients born at Sainte-Justine UHC and identified through the neonatal screening program	72	92.3
Missed SCD patients†	6	7.7
Specimen not sent to the laboratory	2	2.6
Inadequate specimen	1	1.3
False-negative result	3	3.8
Confirmation and follow-up within three months		
SCD patients born at Sainte-Justine UHC	67	85.9
SCD patients identified by the screening program	67	93.1

**Total number includes patients born between January 1988 and June 2003 who were identified through the screening program or through the sickle cell disease (SCD) clinic; †The authors were unable to evaluate the possibility of a missed neonatal diagnosis in a patient born at the Sainte-Justine University Health Centre (Sainte-Justine UHC) who never had a subsequent visit to the institution*

at the clinic is composed of a paediatric hematologist, a paediatrician, a specialized nurse, a social worker and other specialists as required. All infants had a confirmatory blood sample obtained by venipuncture and analyzed by the Hb separation technique in use at that time. DNA analyses were not performed. On confirmation of the diagnosis, patients were enrolled in the SCD clinic and received penicillin, folic acid and recommended available immunizations, including immunization against *S pneumoniae*. Parental education about the genetics and pathophysiology of SCD, as well as the need for urgent medical evaluation in the event of fever, pain or acute splenic sequestration, was an integral part of the program. Parents and siblings were also offered testing for sickle cell trait or SCD. When resources were available, appropriate genetic counselling was offered to families of infants with sickle cell trait.

To identify children born at Sainte-Justine UHC who could have been missed by the neonatal screening program, a retrospective review of the medical charts of all patients with SCD disease born between January 1, 1988, and June 30, 2003, and enrolled in the SCD clinic was conducted to identify any SCD patients who were born at this hospital but not diagnosed at birth.

RESULTS

From the time of implementation of the program until June 2003, 9619 infants were screened for SCD. The testing results are shown in Table 1, along with the corresponding diagnoses. Of the 9619 infants tested, 8142 (84.6%) had a normal phenotype (FA); 1012 (10.5%) had sickle cell trait (FAS); 386 (4.0%) had HbC trait (FAC); 36 had sickle cell anemia or HbS-beta^0-thalassemia (FS), and one had HbS-beta$^+$-thalassemia (FSA) (combined FS and FSA, 0.4%); 35 (0.4%) had HbSC disease; and seven (0.07%) were either homozygous for HbC or had HbC-beta^0-thalassemia. Thus, in the population tested, a total of 72 newborns (one in 134) were found to have SCD on initial screening.

Of these 72 infants, 67 (93.1%) were seen within 10 weeks of birth and the diagnosis of SCD was confirmed; penicillin prophylaxis was begun at the time of the first clinic visit. Five infants with a positive neonatal screening result were not initially enrolled in the SCD clinic. These children were later referred to the clinic by their treating physician or following a visit to the Sainte-Justine UHC emergency department. Their ages at the time of referral to the clinic ranged from four months to 3.6 years. Of the five infants, one infant was not enrolled until nine months of age because the parents did not come to the clinic, even though numerous contacts were made by the clinic team; for four children, the chart review did not reveal why they were not enrolled in the clinic after birth.

The chart review revealed that six additional children with SCD born at Sainte-Justine UHC during the 15.5-year period covered in the present report were not identified by the newborn screening program (Table 2). Of these six children, there were three for whom false-negative results were recorded – one patient with HbS-beta^0-thalassemia and two with HbSS; their sample results were reported as FA, FAS and FAS, respectively. The reason for these false-negative results could not be determined by retrospective chart review but presumably resulted from either laboratory error or sampling error (ie, specimen from the incorrect patient sent to the laboratory). Of the other three children, there was one (a patient with HbSC) for whom the sample was inappropriate (clotted) and no repeat sample was requested, and two (one each with HbSS and HbSC) for whom blood samples were not sent to the laboratory. Both parents of the latter two neonates were African-American. One of these neonates had neonatal asphyxia and it is possible that blood was not drawn because of the infant's critical clinical condition. The other patient was born prematurely by cesarean section and the chart mentioned that no cord blood was available for the SCD screening test. The ages of the six children at the time of referral to the SCD clinic ranged from 3.5 months to 6.3 years (median

age 12 months). Two of these patients were diagnosed because their siblings had SCD and neither of them had experienced any adverse outcomes before the diagnosis was made. The remaining four infants were diagnosed when they were hospitalized for pneumonia or episodes of severe pain (2). The chart review revealed that all four infants had experienced either pain episodes or infections before their diagnosis of SCD. Although treatment before diagnosis was suboptimal or absent for each of these four children, none had serious adverse outcomes.

Although the cost of this screening program was not determined specifically, it is estimated that, based on screening 1000 patients per year, the cost to perform the Hb analyses (ie, technologist time, reagent costs and equipment depreciation) is approximately $30,000 per year.

DISCUSSION

More than 30 years have elapsed since the first North American newborn screening program for SCD was implemented in New York in 1975 (18). Since then, studies have consistently shown that newborn screening for SCD is associated with decreased mortality and morbidity in these patients (17-21). Furthermore, SCD fulfills all the criteria for neonatal screening as defined by the Association of Public Health Laboratories and the Council of Regional Genetic Networks (27). Widespread neonatal screening for SCD has been widely implemented for several years in the United States; however, no provincial screening programs for SCD, either universal or targeted, exist anywhere in Canada, even in those regions with significant numbers of at-risk infants.

Following the 1987 publication of the Consensus Development Panel guidelines (5), a targeted screening program for SCD was established at Sainte-Justine UHC, our mother-child tertiary care hospital. Over a 15.5-year period, the screening program successfully identified 92.3% of infants with SCD who were born in our hospital and who were subsequently followed in our clinic. While this compares favourably with the 80% identification rate reported in the literature for targeted programs (28), the fact that at least six children with SCD born in our institution were not identified by the program highlights the problems of a targeted screening program. In addition, we do not know whether there were other newborns with SCD born in our hospital who were not identified by our screening program and who never came to our attention because they never returned to our hospital. Targeted screening programs for SCD may miss patients for the following reasons: patients at risk for SCD who are not of African descent may not be screened (for example, a newborn screening pilot study [23] for hemoglobinopathies in the Montreal area showed that 24% of HbS genes were in neonates from Central America descent, and in our own SCD clinic, 5.9% of patients are from non-African ancestry); some black infants do not have obvious pigmentation at birth and may not be tested, particularly if the mother is not black; a targeted screening program relies on medical and laboratory personnel's knowledge that such a screening program does exist and the importance of the program; and there is no systematic follow-up when appropriate specimens are not sent to the testing laboratory. A universal program would obviously alleviate the problem of targeting at-risk patients according to their ethnicity. Screening for SCD can be performed using dried blood spot specimens and, therefore, could be performed using the same specimens used for the current neonatal screening program. Furthermore, the mechanisms already in place to inform and provide adequate follow-up in designated clinics to patients diagnosed through provincial neonatal screening programs could also be used for SCD patients.

Cost-effectiveness studies show that universal screening programs always identify more children with diseases and prevent more deaths than targeted screening programs but that cost-effectiveness depends on the proportion of the population at risk (29). This principle applies to SCD screening (27). A cost-effectiveness analysis by Sprinkle et al (30) proposed that the demographic threshold for cost-effectiveness occurs when the proportion of African-American live births in a given population in the United States reaches approximately 5%. In the 2001 Canadian census, the proportion of black people in the Montreal metropolitan area was 4.1% (31). However, the proportion of live births by ethnic origin is not reported. In the targeted population served by Sainte-Justine UHC, the birth prevalence of SCD was one in 134, which is higher than the one in 400 prevalence of SCD reported in African-Americans (5). These data lead us to believe that SCD universal screening may be cost-effective in certain Canadian regions.

A Canadian pilot study (23) conducted in the greater Montreal area between 1987 and 1988, in which 2279 cord blood specimens obtained from nine different ethnic groups were analyzed, estimated the prevalence of HbSS to be 40 per 100,000 newborns in this nontargeted population. During a 15.5-year period, our program identified 72 SCD newborns among 9619 screened newborns (749 per 100,000) in a targeted population in the same geographical region. While the targeted nature of the program at Sainte-Justine UHC does not permit a direct comparison between currently existing neonatal screening programs and the number of affected infants that could be identified by a universal screening program for SCD, the results of our program and the previous study conducted in Montreal do suggest that clinical efficacy and cost-effectiveness would likely compare favourably with existing programs. For example, the Quebec Network of Genetic Medicine reported 48 cases of phenylketonuria and 67 cases of tyrosinemia in 1,054,950 newborns (prevalences of 4.5 and 6.4 per 100,000 newborns, respectively) screened in Quebec between 1969 and 1983, and 197 cases of congenital hypothyroidism in 915,112 newborns (prevalence of 22.2 per 100,000) screened between 1974 and 1983 (32). Thus, the absolute numbers of infants identified in our single hospital program was greater than the number of infants identified by province-wide universal screening programs

for phenylketonuria or tyrosinemia over time periods of approximately the same length.

Our experience with this targeted neonatal screening program shows that such a program is feasible even with limited resources. Our screening program had a very good, positive predictive value, with all of our positive screening test results being subsequently confirmed to be true positives. More important, our screening program was clinically effective because it led to the identification of 92.3% of at-risk patients born at our hospital who were ultimately enrolled in our multidisciplinary SCD clinic. All of these infants began receiving appropriate medical care before 10 weeks of age as opposed to infants not identified by the screening program who only began receiving treatment (in particular, penicillin prophylaxis) at a median age of 12 months. We propose that, as a minimum, targeted neonatal screening should be available to all newborns at risk for SCD in Canada. Furthermore, the cost-effectiveness of a universal neonatal screening program for SCD in regions with a multiethnic population should be studied.

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AUTHORS' NOTE: At the time of publication, all American states, except one, have implemented a universal screening program for SCD (<http://genes-r-us.uthscsa.edu/nbsdisorders.htm>). In Canada, in November 2005, the province of Ontario announced that it will begin neonatal screening for SCD in 2006 (<http://ogov.newswire.ca/ontario/GPOE/2005/11/02/c9618.html?lmatch>).

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