Current Sickle Cell Screening Program for Newborns in New York City, 1979–1980

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Abstract: The newborn screening program mandated by the New York State Public Health Law requires that every baby born in the state be tested for eight conditions including sickle cell anemia. Although sickle cell screening of newborns has been in operation since 1975, the follow-up program for case retrieval to obtain repeat blood samples for definitive diagnosis and referral of diagnosed patients for ongoing medical care was established only in 1979. Of the 106,565 blood samples tested in New York City Newborn Screening Laboratory, March 1, 1979 to February 29, 1980, 141 infants were identified on repeat blood testing as having various forms of sickle cell disease (SS, SC and Sβ-Thalassemia) and were referred for ongoing medical care. Data received on 131 patients from follow-up clinics revealed that the disease diagnosis made by the Newborn Screening Laboratory was confirmed in all patients. There were no deaths reported among the study patients (131 infants) followed for the period of 8–20 months despite the life-threatening complications among eight patients. Binomial distribution of the data on Black infants according to the Hardy-Weinberg equation showed reasonable agreement between the observed and computed incidence of various forms of sickle cell disease. (*Am J Public Health* 1983; 73:249–252.)

Introduction

In recent years, the list of genetic diseases for which early diagnosis and treatment is available has grown exponentially. One significant outcome of these advances in medical technology and clinical acumen has been the spread of newborn screening programs for early detection of treatable disorders. Currently, 48 states in the United States are involved in testing newborns for one or more conditions.[1]

New York State's newborn screening program was established in 1964 by legislation mandating testing for phenylketonuria.[2] Ten years later, the program was expanded to provide testing for six more conditions, including homozygous sickle cell disease. The rationale for screening for sickle cell disease at birth is to prevent early mortality among these infants by ensuring immediate referral of diagnosed infants to programs structured for their care. Deaths occurring in infancy and early childhood can be prevented if the life-threatening complications of the disease—namely acute splenic sequestration crisis and bacterial sepsis—are diagnosed and treated early and aggressively. Preventive methods utilizing blood transfusions and prophylactic antibiotics, among other things, may also be used in appropriate cases. Crucial to the management is the ongoing education and counseling of the parents of these children.

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Under the New York State Public Health Law, all newborns are required to be screened for sickle cell disease of homozygous variety (SS); however, the screening procedures employed in the newborn screening laboratory identify the infants born with various other forms of sickle cell disease (SC, Sβ-Thalassemia, SD, SO^{Arab}) and other hemoglobinopathies (CC, Cβ-Thalassemia, AS, AC) as well.

In the early phase of the sickle cell screening program in New York City, of 110,000 initial blood samples tested in the newborn screening laboratory, 440 required repeat testing for definitive diagnosis. However, only 227 (52 per cent) of requested samples were received in the screening laboratory to verify the original diagnosis.[3] The major reason for this failure was lack of funds and facilities for outreach services and the follow-up of presumptive positive cases. In 1979, with funds available from the New York State Genetics Grant, a follow-up program was established in the New York City Department of Health. In addition, effective communication was established between the follow-up program and the hospitals willing to participate in the follow-up of their identified newborns.

The purpose of this paper is to report:

- Our experience with sickle cell screening of 106,565 newborn samples and with follow-up of various forms of sickle cell disease patients identified in New York City during a one-year period (March 1, 1979 to February 29, 1980);
- The relative frequency of major hemoglobin disorders at birth in New York City;
- The reliability of the micro-techniques used in the screening laboratory to diagnose sickle cell disease at birth; and
- The relationship of the early institution of comprehensive medical care to eventual outcome in the newborns identified with various forms of sickle cell disease.

TABLE 1—Incidence of S and C Hemoglobinopathies among Black Newborns in New York City and the United States

Live Births (3/1/79–2/29/80) Screening Laboratory Diagnoses	Total 106,223	Black 37,138 (35.0%)	Incidence (%) among NYC Black Newborns 3/1/79–2/29/80	Estimated Most Likely Incidence (%) among US Black Newborns**
Disease	149	135 (91%)	—	—
SS	79	[69] (87%)	0.19 [66]* (0.18)*	0.16
Sβ-Thal	14	[14] (100%)	0.04 [16]* (0.04)*	0.06
SC	47	43 (91%)	0.12	0.12
SD	1	1 (100%)	0.003	—
CC	7	7 (100%)	0.02	0.02
Cβ-Thal	1	1 (100%)	0.003	0.02
Trait				
AS	3,473	2,591† (75%)	7.0	8.0
AC	884	781† (88%)	2.1	3.0

*Data modified after additional testing and family study done in follow-up clinics (See Table 3).
**Source: Reference 8.
†Based on 10% sample.

Materials and Methods

Each baby born in New York City has a Guthrie filter paper blood specimen taken by heel prick, usually on the 3rd day of life or on the day of discharge from the hospital.[4] Since almost all babies born in New York City are born in hospitals, the hospital is responsible for checking the blood specimen for its adequacy, recording the information required on the blood collection laboratory form provided by the New York City Newborn Screening Laboratory, and mailing the blood sample to the Newborn Screening Laboratory within 24 hours of collection. Information regarding prematurity and administration of blood transfusion before the time of heel prick is requested but is not uniformly provided.

Each filter paper blood specimen is processed in the Newborn Screening Laboratory, usually on the day of arrival of the specimen. Four discs are punched out in a circle on filter paper and an hemolysate prepared from the punched out discs is tested by hemoglobin electrophoresis on cellulose acetate.[5] Specimens with abnormal hemoglobin on cellulose acetate electrophoresis are further tested by citrate agar electrophoresis.[5] A presumptive positive diagnosis is made when the major amount of hemoglobin detected on citrate agar electrophoresis is either abnormal or undefined, and a letter requesting a repeat blood specimen (micro-capillary) is then sent by the screening laboratory to the physician in the hospital of birth. If the hospital of birth indicates that it would be unable to obtain a second sample of blood on an infant with a presumptive positive test result, an outreach worker from the New York City Follow-Up Program contacts the infant's parents directly and collects a repeat blood sample either at home or in the central office.

Repeat samples are also processed in the Newborn Screening Laboratory. When the test result on a repeat specimen reveals hemoglobin (Hgb) S without Hgb A, or Hgb S and C, or Hgb S with minimal Hgb A on citrate agar electrophoresis, the screening diagnosis of a form of sickle cell disease is finalized; arrangements for appropriate follow-up of the infant, through a hematology clinic, sickle cell clinic, or private physician is then made with concurrence of the parents.

Thirty-four participating hospitals carry out their own follow-up and arrange for subsequent medical care of their patients. These hospitals not only provide comprehensive medical care to their patients but also notify the Follow-Up Program regularly about the status of all infants.

Results

During the study period (March 1, 1979 to February 29, 1980), there was a total of 106,223 live births in New York City and 106,565 initial blood specimens were received to be tested for sickle cell in the New York City Newborn Screening Laboratory. The results of initial testing revealed 3,473 infants with sickle cell trait (AS), 884 with C trait (AC), 152 as presumptive positive for homozygous sickle cell disease or various other forms of sickle cell disease, and 8 for CC disease.*

Of the 152 presumptive positive infants, 144 were retested in the newborn screening laboratory and 141 had the original diagnosis confirmed; 79 were found to have SS, 47 SC, 14 Sβ-Thalassemia, and 1 SD (Table 1). The remaining three cases were diagnosed as trait hemoglobinopathies and the parents were counseled appropriately.

Eight of the 152 infants with presumptive positive diagnoses were not retested. Three families refused retesting, even though in one family this was the second child with SS disease. Five of the eight families could not be located despite our best efforts.**

*Seven of the eight infants were found to have CC and one Cβ-Thalassemia on retesting.

**Since then, our experience with the Follow-Up Program has improved considerably. Presently the program has been successful in reporting the diagnosis to almost all families of presumptive positive newborns.

TABLE 2—Hardy-Weinberg Statistics for Hemoglobinopathies in Black Newborns, New York City, March 1, 1979–February 29, 1980

S gene frequency (Ps)* = 3.8% C gene frequency (Pc)* = 1.1%	Frequency (%)	
Genotype	Observed	Computed
SS	0.18**	0.14 = Ps^2
SC	0.12	0.08 = 2 Ps Pc
CC	0.02	0.01 = Pc^2

$$*Ps = \frac{2 \times SS + S\beta\ THAL + SC + SD + AS}{2 \times \text{Black live births}}$$

$$Pc = \frac{2 \times CC + SC + C\beta\ THAL + AC}{2 \times \text{Black live births}}$$

**Based on the diagnoses reclassified by the follow-up of clinics.

TABLE 3—Analysis of Data Received on Patients Followed for 8–20 Months Period in New York City

Patient Data	No.
Sickle Cell Disease (SS, SC, Sβ Thal)	
Newborns Referred	141
Follow-up Data Received	131 (93%)
Diagnosis Reclassified by Follow-up Clinics	9*
Serious Complications Diagnosed among the Study Patients	8
Salmonella Bacteremia and Osteomyelitis	1
Possible Sepsis	3
Acute Splenic Sequestration Crisis	2
Pneumonia	2
Deaths	0

*Five SS newborns were reclassified to have Sβ Thal; three Sβ Thal to have SS; and one SS to have S/HPFH on follow-up testing of infants and their families.

Analysis of data in relation to sex incidence among the 152 presumptive positive infants revealed that 50.7 per cent were male; of the 3,424 AS*** infants, 50.9 per cent were male. The male-female ratio of 1.03 was similar to the male-female ratio (1.04) reported among live births in New York City during the same period. Female preponderance of Hgb S as reported by Kramer, *et al,* was not observed in our group.[6]

The incidence of sickle cell disorders is known to be highest among Blacks. Of the 106,223 live births in New York City during the study period, 37,138 (35 per cent) were recorded on the birth certificates to be Black.[7] A review of birth certificates of all newborns with disease hemoglobinopathies and 10 per cent samples of those diagnosed with trait hemoglobinopathies produced estimates showing that 91 per cent of all sickle cell disease infants were recorded as Black, the percentage varying from 87 per cent for SS to 100 per cent for Sβ-Thalassemia and CC (Table 1). The majority of non-Black infants were classified as Hispanic on their birth certificates. Only rarely was the race of the infant recorded as White, Oriental or unspecified, and none of the diseased (SS) infants was recorded as White.

The incidence rates were estimated to be 0.19 per cent for SS, 0.12 per cent for SC, 0.04 per cent for Sβ-Thalassemia, and 0.02 per cent for CC. Similary, incidence calculated for AS was 7.0 per cent and for AC 2.1 per cent. These results are comparable with estimates which have been reported for the United States (Table 1).[8]

Binomial distribution of the data on Black infants according to the Hardy-Weinberg equation shows a gene frequency (Ps) of 3.8 per cent for hemoglobin S and a gene frequency (Pc) of 1.1 per cent for hemoglobin C.[9] The computed disease incidence rates for SS, SC, and CC as shown in Table 2 are compared with observed rates. Differences between the observed and theoretical rates may be attributed to: the lack of a precisely defined Black newborn population, mating between members of different ethnic groups with different hemoglobin gene frequencies, insufficient sample size used to identify Black infants with trait hemoglobinopathies to compute disease incidence, and occasional inaccurate recording of race on birth certificates.

Of the 141 infants referred for comprehensive medical care, follow-up data were received on 131 (93 per cent) (Table 3). Of the 131 infants followed over a period of 8–20 months, eight had life threatening complications associated with sickle cell disease and all were treated successfully.‡

Based on the family study and retesting of 131 infants in the follow-up clinics, nine infants had their diagnoses reclassified. Five newborns with SS were reclassified as having Sβ-Thalassemia, and three with Sβ-Thalassemia were reclassified as having SS. One infant initially diagnosed as SS was reported to have sickle hereditary persistent fetal hemoglobin (S/HPFH). His father was the carrier of HPFH.

Two newborns were misdiagnosed (AS instead of AA and AA instead of AS) because of transfusion therapy given prior to the heel prick. One family was inadvertently sent a letter of AC instead of AS by the newborn screening laboratory. Nevertheless, during the study period, not a single infant with sickle cell disease was reported to have trait hemoglobinopathy on subsequent testing in the follow-up clinics. Similarly, no infant was reported to have missed screening at birth and subsequently found to be positive for a hemoglobinopathy.

Discussion

Our experience with sickle cell screening of newborns demonstrates that the methods employed for sickle cell screening at birth are reliable. Hardy-Weinberg statistics further substantiate that the screening tests used are sensitive and reliable.

The importance of mass screening for sickle cell has not been fully accepted. Most would concede, however, that in

***Sex information on 49 AS infants was not available.

‡One infant was treated for Salmonella bacteremia with osteomyelitis, three were admitted with possible sepsis, two had acute splenic sequestration crisis and were transfused, and two were hospitalized for pneumonia.

order to study the natural history of sickle cell disease and to provide adequate resources and funds for effective means of preventive and primary care services, it is necessary to establish incidence and prevalence of the disease. Although the literature dealing with sickle cell disease is voluminous, little information is available regarding the precise incidence of sickle cell disease in a large newborn population in the United States.

Several studies from the United States and elsewhere have reported a death rate of 13–14 per cent among SS patients under the age of two years,[10-12] the principal causes of mortality being bacterial infections and acute splenic sequestration crisis. No deaths were reported among the study patients (131 infants) followed over the period of ages 8 months to 20 months despite the serious life-threatening complications diagnosed in eight infants. Absence of mortality in the study group could be attributed to the comprehensive care given to these patients and their families.

The Sickle Cell Screening Follow-Up Program in New York City has served a dual purpose: first, to ensure early institution of comprehensive medical care for the affected infants, hopefully to reduce mortality in early infancy, and second, to educate their parents with regard to the early detection of signs and symptoms of serious complications of sickle cell disease and the need to contact their physician for prompt medical intervention.

With the recent availability of safe, reliable, and improved techniques for antenatal diagnosis of hemoglobinopathy in the fetus,[13] proper and nondirective counseling of these parents is of paramount importance to assist them in making an intelligent and informed decision regarding future pregnancies.

The Committee for the study of Inborn Errors of Metabolism of the National Academy of Sciences has recommended that, because of diverse motivation of personnel involved in newborn screening, an agency with specific goals should be established in pursuit of an efficient and effective newborn screening program.[14] The goals of this agency should be initial testing of all newborns, case retrieval for definitive diagnosis, treatment and follow-up of identified patients, counseling of identified families, and education of professionals and the lay public. The New York City Follow-up Program for Sickle Cell Screening of newborns has successfully achieved the principal goals noted.

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Abbreviations

Hgb—Hemoglobin
SS—Sickle Cell Disease (homozygous)
Sβ-Thal—Sβ-Thalassemia
S/HPFH—Sickle Hereditary Persistent Fetal Hemoglobin
SD—Sickle D Disease
AC—C Trait
AS—Sickle Cell Trait