Impact of a Comprehensive Sickle Cell Center on Early Childhood Mortality in a Developing Country: The Jamaican Experience

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Objective To compare mortality in children <5 years of age with sickle cell disease (SCD) in Jamaica, a resource-limited country, diagnosed by newborn screening and managed in a comprehensive care facility, to that of the general population.

Study design The study was carried out at the Sickle Cell Unit in Kingston, Jamaica. We determined the status (dead/alive) at age 5 years in a cohort of 548 children with SCD diagnosed by newborn screening and managed at the Sickle Cell Unit during the period November 1995 to December 2009. The standardized mortality ratio was calculated using World Health Organization life tables for reference mortality.

Results Eight deaths (1.5%) occurred in children <5 years of age during the study period. The mean age at death was 2.0 ± 1.5 years. The overall mortality incidence in children <5 years of age was 3.1 (95% CI 1.6, 6.2) per 1000 person-years with a standardized mortality ratio of 0.52 (95% CI 0.3, 1.0).

Conclusions Mortality in children <5 years of age with SCD diagnosed at birth and managed at a comprehensive care clinic in Jamaica is equivalent to that of the general population. Children with SCD, a highly vulnerable population, can be effectively managed, even in resource-limited environments. *(J Pediatr 2015;167:702-5)*.

Jamaica is a small, middle income, developing island state in the Caribbean. It is a resource-limited, highly indebted country with the fourth highest debt to gross domestic product ratio in the world.[1] Sickle cell disease (SCD) is a global problem and poses a major health burden for countries such as Jamaica, as well as sub-Saharan Africa where the prevalence is highest. An estimated 300 000 infants per annum are born worldwide with the disease, ~75% being born in sub-Saharan Africa.[2] In Jamaica, the birth rate has fallen from ~47 000 in 2002 to ~ 36 700 in 2013.[3] SCD occurs in every 1:150 infant births with homozygous SCD (HbSS) being the most common variant, occurring in every 1:300 infant births.[4] Children with SCD are particularly vulnerable in the early childhood period. Early childhood mortality rates from 50%-90% have been reported in children with SCD in sub-Saharan Africa, specifically among children with homozygous SCD (HbSS).[5,6] Prior studies in Jamaica have shown improvement in cumulative survival in children <5 years of age with SCD, who were managed in a comprehensive care facility, from 81% to 98%.[7,8]

The United Nations millennium development goal number 4 has as its aim the reduction in mortality of children <5 years of age by two-thirds between 1990 and 2015.[9] It is estimated that SCD may be responsible for 5%-16% of mortality in children <5 years of age in some areas of sub-Saharan Africa.[2] In a hospital-based study in Tanzania, Makani et al[10] reported mortality rates in children <5 years of age with SCD as 7.3 per 1000 person-years (standardized mortality ratio [SMR] of 2.9).

In Jamaica, mortality of children <5 years of age decreased by ~14% from 1990-2005.[1] Although further improvements continue with ~56% reduction from 1990-2013, it still lags behind its millennium development goal target.[11] With the introduction of newborn screening (NBS) for SCD and improvements in comprehensive care, mortality in children <10 years of age with SCD has decreased from 17.6%-1.8%.[7] Comprehensive care allows for implementation of early-life interventions. In Jamaica, for children <5 years of age, this includes routine health visits every 3 months, disease-specific education, and health promotion, including but not restricted to fever management, splenic palpation, and penicillin prophylaxis. Penicillin prophylaxis is, for the most part, given intramuscularly every 28 days with good compliance.[12] In addition, pneumococcal polysaccharide vaccine is administered at age 4 years and since 2010, pneumococcal conjugate vaccine has been routinely administered to children <5 years of age. Within the context of these public health measures, it remains unknown whether SCD contributes to excess mortality in children <5 years of age in Jamaica.

As such, the aims of this study were to compare mortality in children <5 years of age with a severe form of SCD—homozygous SCD (HbSS) or sickle β^0-thalassemia (HbSβ^0) disease—diagnosed by NBS and managed in a comprehensive care facility, to mortality in children

JamSCUB	Jamaica Sickle Cell Unit Birth
NBS	Newborn screening
SCD	Sickle cell disease
SCU	Sickle Cell Unit
SMR	Standardized mortality ratio

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<5 years of age in the general population and also to determine if any sex difference existed.

Methods

The Sickle Cell Unit (SCU), Kingston, Jamaica, the only comprehensive sickle cell clinic in the English-speaking Caribbean, operates a free clinic from Monday to Friday for the over 5000 patients registered in its database. Patients are currently either referred to the unit or recruited from its NBS program that started in November 1995 and screens ~40% of births island wide.[7] The clinical service is guided by local clinical care guidelines[13] and includes health maintenance, management of acute and chronic problems, and specialty clinics. It has an 8-bed day care ward but no in-patient facility. Patients requiring in-patient care are referred to the nearest hospital to be managed by the relevant hospital team. The clinic is staffed primarily by pediatricians, family doctors, and registered nurses. There was a hematologist attached to the unit from January 2006 through July 2014. A laboratory service provides SCD diagnosis using hemoglobin electrophoresis, and basic hematology investigations including complete blood count and reticulocyte count. In addition, the unit provides a consultancy role for persons with SCD being managed in other institutions. Ethical approval was obtained from the the University Hospital of the West Indies/The University of the West Indies, Faculty of Medical Sciences Ethics Committee.

The current NBS program in Jamaica started in November 1995. Children with a confirmed diagnosis of severe form of SCD are enrolled into a birth cohort, the Jamaica Sickle Cell Unit Birth (JamSCUB) cohort. Screening and recruitment processes have been described before.[7] In summary, after initial cord blood screening at birth, babies whose screen results were suggestive for SCD were brought back at ~age 3 months for confirmatory testing. If confirmed to have SCD, babies would then begin care at the SCU. As of October 2011, there were 609 children enrolled in JamSCUB cohort.

This was a retrospective analysis of death data. Children from JamSCUB cohort were eligible if they were born between November 1, 1995, and December 31, 2009, and were managed at the SCU in Kingston, Jamaica. We sought to determine the status (dead or alive) of each eligible child at age 5 years. If a child defaulted from follow-up before their fifth birthday (N = 63), a death registry search was done at the Registrar General's Department, where vital statistics are registered in Jamaica. No child who had defaulted was found to have been registered as a death. Likewise, if a child had migrated before the age of 5 years, information on the child's status was obtained by contacting relatives.

Children were excluded if: (1) they were born after December 31, 2009 (N = 15); (2) after screening they were confirmed to have SCD (~age 3 months), but had never attended the clinic for a first doctor's visit and so were never managed at the SCU (N = 45); or (3) they had emigrated before the age of 5 years and further information about their status could not be determined (N = 1).

Statistical Analyses

World Health Organization life table data for Jamaica were used for reference mortality. This provided data from January 1, 1990 to December 31, 2009, hence, the reason the analytical sample was restricted to children born before January 1, 2010. The analytic period started at date of birth and ended at date of fifth birthday or date of death. Overall mortality rate and age-specific mortality rates were calculated from the ratio of number of deaths divided by the number of person-years of observation. The SMR, the mortality rate among the cohort (observed number of deaths per person-years) relative to the expected mortality rate in the general population of Jamaica (expected number of deaths per person-years) was calculated. The expected number of deaths was estimated by multiplying the survival time accrued from the cohort by the mortality rates of the general population matched by age bands (<1 year of age and 1-5 years of age), sex, and calendar period (10 years, 1990-1999 and 2000-2009). To account for the possible error in assuming that all 63 children who had defaulted before their fifth birthday were alive at 5 years, 2 further analyses were done using 2 models. The first assumed that the mortality experience in the defaulters was similar to that in the first one-third of the Jamaica Sickle Cell Cohort Study, when stratified according to date of birth (enrollment period)[4,8] (ie, 17%). The second model (model 2), assumed a similar mortality rate in the defaulters of 1% as in the current nondefaulting cohort. Patients were randomly selected to determine who had "died." The date of death was taken as the midpoint between their last visit and their fifth birthday.

Data were analyzed using Stata v 12 (StataCorp, College Station, Texas).

Results

Of 548 children eligible for the study (**Figure**; available at www.jpeds.com), 8 deaths (1.5%) occurred in children <5 years of age during the study period. All deaths occurred in children with HbSS (M:F = 5:3). The mean age at death was 2.0 ± 1.5 years (range 0.7-4.9 years). Three (37.5%) deaths, all male children, occurred before the age of 1 year. Four (50.0%) deaths occurred in each calendar period, 1990-1999 and 2000-2009 (**Table I**).

The primary causes contributing to death were: (1) acute anemia (n = 5), acute splenic sequestration (n = 2), and aplastic anemia (n = 1); (2) acute chest syndrome (n = 2); (3) suspected sepsis (n = 1); and (4) sudden unexplained event (n = 1). One child had 2 diagnoses contributing to death.

The 548 children provided 2566 person-years of observation (female: 1346 person-years of observation). The overall mortality incidence in children <5 years of age was 3.1 (95% CI 1.6, 6.2) per 1000 person-years. The highest mortality incidence, 5.5 per 1000 person-years, occurred before the age of 1 year (**Table I**).