# Population-Based Study to Determine Mortality in Spina Bifida: New York State Congenital Malformations Registry, 1983 to 2006

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Background: The lifetime risk of death among individuals with spina bifida is 10-times higher compared with the general population. A population-based analysis on cause-specific mortality among individuals spina bifida is lacking. Methods: Using statewide, population-based New York Congenital Malformations Registry, we examined all births between years 1983 and 2006, and identified 1988 births with spina bifida and 10,951 births with congenital hypertrophic pyloric stenosis (CHPS). We linked registry records to birth and death files from vital records, and determined age- and cause-specific mortality for isolated and multiple spina bifida, and compared the findings with the less fatal CHPS. Results: Mortality in spina bifida is significantly high compared with CHPS (16.9% vs. 0.96%, respectively). The probability of survival in spina bifida was lower compared with CHPS. A majority of the deaths in spina bifida occurred in infants within the first year of birth; however, an increased risk of death persisted in young adulthood for both isolated and multiple cases of spina bifida. The common causes of death in children with spina bifida were hydrocephalus, infections, cardiac anomalies, pneumonia, and pulmonary embolism; while infections, heart or kidney failure, injuries and neoplasms contributed to deaths in adults. Conclusion: We conclude that mortality in spina bifida is a large concern, and individuals living with the defect require improved clinical care for lethal medical complications. Primary prevention of spina bifida through mandatory folic acid fortification remains as the best strategy to reduce both disability and mortality associated with this defect across the world.

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**Key words:** birth defects; cause of death; congenital malformations registry; hypertrophic pyloric stenosis; long-term follow-up; mortality; spina bifida

## Introduction

Spina bifida is a major congenital disorder of the central nervous system and is associated with severe motor, sensory and structural abnormalities (Sandler, 2010). It is commonly accompanied by hydrocephalus, marked by an abnormal accumulation of cerebrospinal fluid in the brain cavity (Sandler, 2010). According to the Centers of Disease Control and Prevention, approximately 3000 babies are born with spina bifida each year in the United States (US), and an estimated 150,000 children and young adults live with the condition. Thus, a significant number of affected individuals seek complex health services and are experiencing the burden of morbidity and mortality associated with spina bifida (Burke and Liptak, 2011; Rowe and Jadhav, 2008). The estimated average lifetime medical cost of spina bifida care is up to $635,000 in the United States (Waitzman et al., 2005). Early intervention costs, particularly among infants and children, are 13 times greater in spina bifida compared with those without (Ouyang et al., 2007). Overall, spina bifida has a significant impact on the affected family, and on the health care system (Burke and Liptak, 2011).

Fortunately, both survival and life-expectancy in infants born with spina bifida has improved significantly since the 1960s, owing to advanced neurosurgical and therapeutic interventions (Laurence, 1974). Current estimates show approximately a 80% survival rate among infants born with spina bifida immediately after birth (Oakeshott et al., 2010); and among those that survive, a majority (87–90%) live until at least 1 year (Nembhard et al., 2001; Bol et al., 2006; Wang et al., 2011). However, the survival rate decreases at later ages due mostly to complications associated with spina bifida (Shin et al., 2012; Bowman et al., 2001). Sex, age, race and ethnicity, low birth weight, level of the lesion, presence of other birth defects, and birth year are associated with increased mortality in spina bifida (Wong and Paulozzi, 2001; Wang et al., 2011; Shin et al., 2012). One study has shown that the relative risk of death among children with spina bifida is 10 times (95% confidence interval [CI] = 7.5, 13.5) greater than children without birth defects, at age 6 years or older (Wang et al., 2010).

Few studies have explored underlying causes of death in spina bifida (Table 1). The majority of these studies used data collected from regional referral hospitals that may not have represented all cases of spina bifida in their respective population. Only one study in the United Kingdom has examined the causes of death in a large community-based cohort of infants born with spina bifida, who were nonselectively operated for open spina bifida at

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**TABLE 1.** *Previous Literature on Mortality and Cause of Death in Individuals with Spina Bifida*

| Author (year) | Location | Outcome | Birth years | Follow-upperiod | Subject Selection | Mean age in years (range) | Total SB live births N | SB live births included in the study | # Deaths at the end of follow-up/ # of cases | Causes of death |
|---|---|---|---|---|---|---|---|---|---|---|
| Haase (1987) | Fyn County, Denmark | SB | 1965–1974 | 7 years | Referral hospital | NS | 33 | 33 | 15/33 | NS |
| Kalucy (1994) | Western Australia | SB (with or without hydrocephalus) | 1966–1990 | 25 years | Referral hospital | NS | 395 | >95% (~) | 204/395 | Ages 1 - 5 years: CNS infections, shunt infection, increased intracranial pressure<br>Ages 6 - 16: Complications from hydrocephalus, renal failure, respiratory causes |
| McDonnell (2000) | Belfast, Ireland | SB | NS<br>Study years 1990–1999 | 40 years | Referral hospital<br>>16 years of age | 28.1 | 280 | 280 | 18/280 | Renal failure, infection, cardiac failure, post-surgery for Chiari malformation, respiratory arrest, possible shunt malfunction, status epilepticus, myocardial infarction, perforated duodenal ulcer, ruptured basilary artery aneurism |
| Bowman (2001) | Chicago, USA | SB | 1975–1979 | 25 years | Referral hospital | 21.7 | 118 | 71 | 28/118 | Infancy – childhood: hind brain dysfunctionYoung adults: unrecognized shunt malfunction |
| Wong (2001) | MACDP, Atlanta, USA | SB | 1979–1994 | 18 years 1979–1996 | Population registry | NS | 235 | 235 | 45/235 | NS |
| Hunt (2004) | Cambridge, UK | SB | 1963–1971 | 38 years | Referral hospital | 35 (30–38) | 117 | 117 | 71/117 | Cardiovascular, renal, hydrocephalus, CNS infections, others |

**TABLE 1.** *Continued*

| Author (year) | Location | Outcome | Birth years | Follow-upperiod | Subject Selection | Mean age in years (range) | Total SB live births N | SB live births included in the study | # Deaths at the end of follow-up/ # of cases | Causes of death |
|---|---|---|---|---|---|---|---|---|---|---|
| Preis (2005) | Gdansk, Poland | SB | 1991–2001 | NS | Referral hospital | NS | 47 | 47 | 25/47 | NS |
| Oakeshott (2010) | Cambridge, UK | SB | 1963–1971 | 38 years | Referral hospital | 35 (30–38) | 117 | 117 | 71/117 | Unexpected deaths (epilepsy, pulmonary embolus, acute hydrocephalus, and acute renal sepsis) |
| Roach (2011) | Texas,USA | SB | 1941–1964 | 45 years~ 1985–1987 | Referral hospital | 31 (20–58) | 221 | 149 | 45/149 | General infection, hydrocephalus, heart failure, kidney failure, unknown reasons |

CNS, central nervous system; MACDP, Metropolitan Atlanta Congenital Defects Program; NS, not stated; SB, spina bifida.

the time of their birth and followed up to age 40 (Oakeshott et al., 2010). Findings from this study showed that approximately one-quarter (26%) of spina bifida survivors died by age 35; and reported a 10-fold greater risk of death in adults with spina bifida compared with the general population. Cause of death in this study was abstracted from multiple sources (e.g., Office for National Statistics, medical records, autopsy, care giver interview, etc.). Overall, 32% of deaths in their cohort were reported as unexpected and sudden, due to underlying causes such as epilepsy, pulmonary embolus, acute hydrocephalus, and acute renal sepsis.

Using data from the Congenital Malformations Registry (CMR) in New York (NY) State, we have examined the underlying causes of death in all births (1983–2006) that were affected with spina bifida in Upstate NY and New York City (NYC), and compared the outcomes to births affected by a less fatal birth defect, the congenital hypertrophic pyloric stenosis (CHPS) during the same birth years and follow-up period as spina bifida cases. We chose to study CHPS as a comparison because it renders the highest probability of long term survival (>99%) among the affected, compared with all other birth defects (Wang et al., 2011). The goal of our study was to assess survival and causes of death in spina bifida. We examined infant and maternal factors associated with mortality among individuals with spina bifida and CHPS; assessed survival probability; and examined the cause of death in the two groups for specific age strata, and by presence or absence of other major birth defects.

## Methods

### DATA SOURCE

The CMR was established by the NY State Department of Health as part of the Environmental Disease Surveillance Program in 1982, by enactment of Part 22 of the NY State Sanitary Code. It is one of the largest statewide, population-based birth defects registries in the United States, and surveys nearly 250,000 live births in NY State each year, including NYC (http://www.health.ny.gov/diseases/congenital_malformations/cmrback.htm; accessed on June 6, 2013). Every physician and hospital attending to an individual diagnosed within 2 years of birth as having one or more congenital anomalies is required to file a supplementary report with the State Commissioner of Health within 10 days of diagnosis. The recorded defects are mainly due to structural, functional or biochemical abnormality, and are determined to be genetic or have occurred during pregnancy. CMR collects and maintains information on a wide range of major structural birth defects of both genetic and nongenetic etiologies. These data have aided past studies on survival experience of infants with birth defects (Wang et al., 2010, 2011). CMR is one of the few registries in the United States that

allows us to study cause of mortality in individuals with spina bifida using record linkage to the death certificate files maintained by the NY State Department of Health. A recent study using CMR data on births between 1983 and 2006 estimated the overall mortality risk (mortality rate ration) for children with spina bifida in NY, by age and selected risk factors (Wang et al., 2010).

We conducted a retrospective review of all births diagnosed with spina bifida or CHPS born between January 1, 1983 and December 31, 2006 in the Upstate NY and NYC; henceforth referred to as NY. The follow-up period began at birth and ended on December 31, 2011. Cases were eligible if the infant had either spina bifida or CHPS, were born during the study period, and if their mother resided in NY. All birth defects were classified using International Classification of Disease (ICD-9) codes (birth years 1983–1991) or British Pediatric Association (BPA) codes (birth years 1992–2006).

We further classified all spina bifida cases as "isolated," "multiple," or "other," based on the presence of other major structural anomalies. The "other" group consisted of cases with known genetic etiology (e.g., trisomy, Turner syndrome, Prader-Willi syndrome, Meckel-Grubel syndrome, cloacal exstrophy, and other miscellaneous syndromes), and were excluded from some of our analyses. We also examined cases by presence or absence of hydrocephalus.

### DATA MATCHING

The CMR routinely matches all infants identified with a birth defect with their vital records (birth and death certificates). This procedure includes deterministic data linkage, using multiple matching variables: infant's first and last name, infant's date of birth, medical record number, mother's last name, mother's date of birth, mother's social security number and residential information, and hospital of birth. The linkage rate between CMR records and birth certificates is very high (97%). CMR ascertained deaths using linked birth and death files from vital records. If they could not locate an individual's death certificate, they assumed the subject was alive. Past studies using the National Death Index have added very few additional deaths.

### STUDY VARIABLES

Spina bifida and CHPS cases were determined using CMR-provided ICD-9 codes (spina bifida: 741.0–741.9; CHPS: 750.5) or BPA codes (spina bifida: 741.000–741.990; CHPS: 750.500–750.580). Information on infant (sex, birth weight, gestational age at delivery) and maternal characteristics (age at delivery, race/ethnicity, education, gravidity) was obtained from birth certificates. Among deceased subjects, we abstracted year and underlying cause of death using ICD-9 codes from the death certificate.

### STATISTICAL ANALYSIS

We compared selected infant and maternal characteristics, and mortality (death, age at death) between all spina bifida and CHPS cases using the Pearson chi-square test or Fisher's exact test (expected cell frequencies $<5$). Unadjusted odds ratios (uOR)s and 95% confidence intervals (CIs) were estimated to investigate the associations between spina bifida mortality and previously mentioned infant and maternal characteristics among isolated and multiple cases only. We used Kaplan-Meier plots to examine survival probability in spina bifida and CHPS.

Specifically for spina bifida cases, we examined number and percent of deaths separately for isolated cases and multiple cases, and reported by age at death (in years) (<1/1–5/6–10/11–15/16–20/21–25/25–28), sex (male/female), maternal race/ethnicity (White/Black/Hispanic), and by presence or absence of hydrocephalus (Yes/No). For spina bifida and CHPS, we examined the frequency of cause of death by isolated and multiple categories, for each age-at-death stratum. For those who were deceased under age 5 years, we reported cause of death with at least 3 reported deaths with a similar ICD-9 code for primary diagnosis.

The data matching and the statistical analyses for the study were performed using the Statistical Analysis System (SAS) software package, version 9.2 (SAS Institute, Cary, NC). The Institutional Review Boards of NY Department of Health and Emory University approved the study.

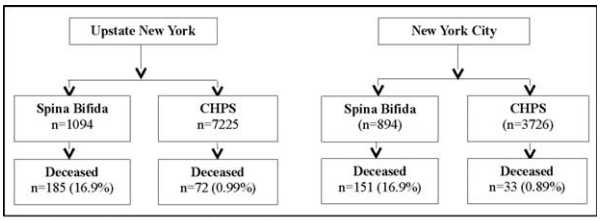



**FIGURE 1.** *Case identification for spina bifida and congenital hypertrophic pyloric stenosis, congenital malformations registry, New York, birth years: 1983 to 2006*.*

## Results

During 1983 to 2006, CMR tracked 1988 births with spina bifida (Upstate NY = 1094; NYC = 894); and of these, identified 336 (Upstate NY = 185; NYC = 151) as deceased during the follow-up period (Fig. 1). During the same time period, there were 10,951 births with CHPS (Upstate NY = 7225; NYC = 3726), and of these, CMR identified 105 as deceased (Fig. 1). We compared infant and maternal characteristics for all spina bifida and CHPS cases by geographic region, i.e., upstate NY and NYC (Table 2). We found significant differences among spina bifida cases between these two regions with respect to birth weight, maternal race, maternal education, and gravity ($p < 0.05$); however, there were no differences between the percent of deaths or the age at death associated with spina bifida. Similar results were noted for

**TABLE 2.** *Infant and Maternal Characteristics, and Mortality of Individuals with Spina Bifida and Congenital Hypertrophic Pyloric Stenosis in New York (Birth Years: 1983 to 2006)*

| | Spina bifida (N=1988) | | | CHPS (N=10951) | | | All spina bifida | All CHPS | |
|---|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **Upstate NY (*n* = 1094)** | **New York City (*N* = 894)** | ***P*** | **Upstate NY (*N* = 7225)** | **New York City (*N* = 3726)** | ***P*** | **All NY (*N* = 1988)** | **All NY (*N* = 10951)** | ***P*** |
| Infant sex | | | | | | | | | |
| Male | 502 (45.9) | 421 (47.1) | | 5943 (82.3) | 3008 (80.7) | | 923 (46.4) | 8951 (81.7) | * |
| Female | 592 (54.1) | 473 (52.9) | | 1282 (17.7) | 718 (19.3) | | 1065 (53.6) | 2000 (18.3) | |
| Birth weight (grams) | | | | | | | | | |
| <1500 | 73 (6.7) | 44 (4.9) | * | 92 (1.3) | 25 (0.7) | * | 117 (5.9) | 117 (1.1) | * |
| 1500–2499 | 132 (12.1) | 158 (17.7) | | 464 (6.4) | 253 (6.8) | | 290 (14.6) | 717 (6.5) | |
| >2499 | 889 (81.2) | 692 (77.4) | | 6669 (92.3) | 3448 (92.5) | | 1581 (79.5) | 10117 (92.4) | |
| Gestational age (months) | | | | | | | | | |
| <37 | 266 (24.3) | 197 (22.8) | | 938 (13.0) | 395 (11.3) | * | 463 (23.7) | 1333 (12.5) | * |
| ≥37 | 828 (75.7) | 666 (77.2) | | 6287 (87.0) | 3087 (88.7) | | 1494 (76.3) | 9374 (87.5) | |
| Missing | 0 | 31 | | 0 | 244 | | 31 | 244 | |
| Maternal age (years) | | | | | | | | | |
| <25 | 384 (35.1) | 343 (38.4) | | 2364 (32.7) | 1461 (39.2) | * | 727 (36.6) | 3825 (34.8) | |
| 25–34 | 586 (53.6) | 438 (49.0) | | 3996 (55.3) | 1806 (48.5) | | 1024 (51.5) | 5802 (53.0) | |
| ≥35 | 124 (11.3) | 112 (12.5) | | 865 (12.0) | 457 (12.2) | | 236 (11.9) | 1322 (12.1) | |
| Unknown | 0 (0.0) | 1 (0.1) | | 0 (0.0) | 2 (0.1) | | 1 (0.05) | 2 (0.1) | |
| Maternal race | | | | | | | | | |
| NH White | 842 (77.9) | 176 (19.7) | * | 6142 (85.0) | 1143 (30.7) | * | 1018 (51.2) | 7285 (66.5) | * |
| NH Black | 101 (9.2) | 259 (29.0) | | 339 (4.7) | 628 (16.9) | | 360 (18.1) | 967 (8.9) | |
| Hispanic | 102 (9.4) | 367 (41.0) | | 521 (7.2) | 1659 (44.5) | | 469 (23.6) | 2180 (19.9) | |
| Other/unknown | 49 (4.5) | 92 (10.3) | | 223 (3.1) | 296 (7.9) | | 141 (7.1) | 519 (4.7) | |
| Maternal education (years) | | | | | | | | | |
| <12 | 198 (18.1) | 296 (34.3) | * | 1140 (15.8) | 994 (28.6) | * | 494 (25.2) | 2134 (19.9) | * |
| 12 | 447 (40.9) | 328 (38.0) | | 2601 (36.0) | 1263 (36.3) | | 775 (39.6) | 3864 (36.1) | |
| >12 | 416 (38.0) | 211 (24.5) | | 3380 (46.8) | 1154 (33.1) | | 627 (32.0) | 4534 (42.4) | |
| Gravidity | | | | | | | | | |
| 1 | 300 (27.5) | 104 (12.1) | * | 2293 (31.7) | 695 (20.0) | * | 404 (20.6) | 2988 (27.9) | * |
| 2–3 | 506 (46.2) | 125 (14.5) | | 3456 (47.8) | 865 (24.8) | | 631 (32.2) | 4321 (40.3) | |
| >3 | 235 (21.5) | 88 (10.2) | | 1267 (17.5) | 411 (11.8) | | 323 (16.5) | 1678 (15.7) | |
| Unknown | 53 (4.8) | 546 (63.2) | | 209 (2.9) | 1511 (43.4) | | 599 (30.6) | 1720 (16.1) | |
| Mortality | | | | | | | | | |
| Yes | 185 (16.9) | 151 (16.9) | | 72 (1.0) | 33 (0.9) | | 336 (16.9) | 105 (1.0) | * |
| No | 909 (83.1) | 743 (83.1) | | 7153 (99.0) | 3693 (99.1) | | 1652 (83.1) | 10846 (99.0) | |
| Age at death (years) | *(n=185)* | *(n=151)* | | *(n=72)* | *(n=33)* | | | | |
| <1 | 107 (57.8) | 84 (55.6) | | 24 (33.3) | 12 (36.4) | | 191 (56.8) | 36 (34.3) | * |
| 1–5 | 36 (19.5) | 44 (29.1) | | 25 (34.7) | 14 (42.4) | | 80 (23.8) | 39 (37.1) | |
| 6–10 | 11 (6.0) | 12 (7.8) | | 3 (4.2) | 3 (9.1) | | 23 (6.9) | 6 (5.7) | |

**TABLE 2.** *Continued*

| Characteristics | Spina bifida (N=1988) | | | CHPS (N=10951) | | | All spina bifida | All CHPS | |
|---|---|---|---|---|---|---|---|---|---|
| | Upstate NY ($n=1094$) | New York City ($N=894$) | *P* | Upstate NY ($N=7225$) | New York City ($N=3726$) | *P* | All NY ($N=1988$) | All NY ($N=10951$) | *P* |
| 11–15 | 12 (6.0) | 6 (4.0) | | 4 (5.6) | 2 (6.1) | | 18 (5.4) | 6 (5.7) | |
| 16–20 | 7 (3.8) | 2 (1.3) | | 7 (9.7) | 1 (3.0) | | 9 (2.7) | 8 (7.6) | |
| 21–25 | 10 (5.4) | 3 (2.0) | | 7 (9.7) | 0 (0) | | 13 (3.9) | 7 (6.7) | |
| 26–28 | 2 (1.1) | 0 (0) | | 2 (2.8) | 1 (3.0) | | 2 (0.6) | 3 (2.9) | |

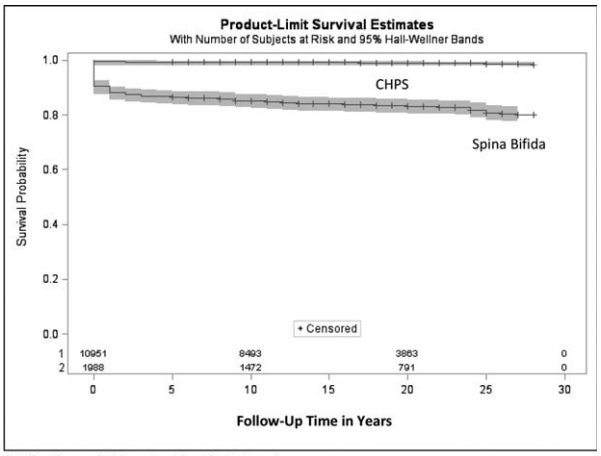
*p* value significant at 0.05. Frequencies of cases in each column may not total, due to missing responses.

CHPS, when comparing the two regions. Next, we proceeded to compare differences between infant and maternal characteristics, as well as mortality and age at death, between all spina bifida and all CHPS cases from both regions of New York State (Table 2). The overall mortality was significantly higher among those with spina bifida compared with CHPS (16.9% vs. 0.96%) ($p < 0.0001$). A majority of deaths in spina bifida occurred in the first year or life (56.8%) (Table 2). Both groups had significant differences in the distribution of infant and maternal characteristics overall (Table 2). Figure 2 shows survival curves of the spina bifida and CHPS during the 28-year follow-up period. The survival probability in spina bifida is lower at all ages compared with CHPS. Furthermore, the survival curve in spina bifida cases declined steeply during the first year, and remained low during the rest of the follow-up period, compared with the survival curve for CHPS.

Of these 336 deaths among spina bifida cases, 182 (54.2%) were classified as having isolated spina bifida, and 93 (27.7%) as multiple spina bifida. The remaining cases, classified as "other", had a genetic or syndromic etiology [Trisomy 18 ($n = 21$), Trisomy 13 ($n = 8$), Meckel-Gruber syndrome ($n = 18$), cloacal exstrophy ($n = 5$), Turner syndrome ($n = 4$), Jeune syndrome ($n = 1$), Prader-Willi syndrome ($n = 1$), and other nonspecific syndromes ($n = 3$)]. Hydrocephalus presented in approximately two-thirds of deceased spina bifida cases ($n = 224$; 66.7%). We noted 105 deaths among CHPS cases, of which 70 (66.7%) were classified as having isolated CHPS, 32 (30.5%) as multiple CHPS, and the remaining three cases had a genetic etiology.

As shown in our unadjusted analysis, mortality in isolated spina bifida cases was positively associated with low birth weight (<1500 g), prematurity (<37 weeks gestational age), and young maternal age at delivery (<25 years), while the association with increased gravidity (>3) was marginally significant (Table 3). Similar associations were found for mortality in multiple spina bifida cases, except there was an additional increased risk associated with increased maternal education (>12 years), and no observable association with gravidity (Table 3).

In our analysis of cause of death among isolated spina bifida cases (Table 4), during the first year of life, prematurity was a noted cause of death in at least 6 cases. For children between 1 and 5 years, apart from hydrocephalus, bronchopneumonia was the second most common cause of death. Cardiac problems contributed to death in children aged 6 to 10 years, and so did respiratory and infectious conditions such as asthma, pneumonia, sepsis, and liver disease. For children aged 11 to 15 years, some notable causes of death included obstructive hydrocephalus, cardiac complications and pulmonary embolism, and pneumonia. For younger adults, primary causes of death included cardiac and central nervous system complications. Of particular interest in the adult age groups are deaths associated with injury and infections. One case had a malignant neoplasm of the bladder reported as the primary cause of death. Results on cause of death analysis in multiple spina bifida cases are presented separately in Table 5. First, among neonates and infants, there were several deaths associated with lung and diaphragmatic problems, apart




CHPS = Congenital hypertrophic pyloric stenosis
*Cases included all spina bifida (N=1988) and all CHPS (N=10,951)

**FIGURE 2.** *Survival probability for spina bifida and congenital hypertrophic pyloric stenosis, New York, birth years 1983 to 2006*.*

**TABLE 3.** *Selected Infant and Maternal Factors Associated with Mortality in Isolated and Multiple Spina Bifida in New York (Birth Years: 1983 to 2006)*

| | Alive Any spina bifida (*n*=1652) | Deceased Isolated spina bifida (*n*=182) | | Deceased Multiple spina bifida (*n*=93) | |
|---|---|---|---|---|---|
| **Characteristics** | ***n* (%)** | ***n* (%)** | **Unadjusted OR (95% CI)** | ***n* (%)** | **Unadjusted OR (95% CI)** |
| Infant sex | | | | | |
| Male | 761 (46.1) | 90 (49.5) | Ref | 41 (44.1) | Ref |
| Female | 891 (53.9) | 92 (50.5) | 0.87 (0.64, 1.19) | 52 (55.9) | 1.08 (0.71,1.65) |
| Birth weight (grams) | | | | | |
| <1500 | 42 (2.5) | 42 (23.1) | 7.59 (4.22, 13.65) | 17 (18.3) | 2.86 (1.44,5.67) |
| 1500–2499 | 205 (12.4) | 27 (14.8) | Ref | 29 (31.2) | Ref |
| >2499 | 1405 (85.1) | 113 (62.1) | 0.61 (0.39, 0.95) | 47 (50.5) | 0.24 (0.15,0.38) |
| Gestational age (weeks) | | | | | |
| <37 | 326 (19.7) | 72 (39.6) | 2.63 (1.91, 3.63) | 40 (43.0) | 3.00 (1.96, 4.61) |
| ≥37 | 1297 (78.5) | 109 (59.9) | Ref | 53 (57.0) | Ref |
| | | | | | |
| Maternal age (years) | | | | | |
| <25 | 589 (35.7) | 80 (44.0) | 1.54 (1.11, 2.14) | 36 (38.7) | 1.19 (0.76, 1.86) |
| 25–34 | 873 (52.9) | 77 (42.3) | Ref | 45 (48.4) | Ref |
| ≥35 | 189 (11.4) | 25 (13.7) | 1.50 (0.93, 2.42) | 12 (12.9) | 1.23 (0.64, 2.37) |
| Maternal race | | | | | |
| Non-Hispanic White | 858 (51.9) | 88 (48.4) | Ref | 43 (46.2) | Ref |
| Non-Hispanic Black | 298 (18.0) | 32 (17.6) | 1.05 (0.68,1.60) | 18 (19.4) | 1.21 (0.68, 2.12) |
| Hispanic | 380 (23.0) | 47 (25.8) | 1.21 (0.83,1.75) | 27 (29.0) | 1.42 (0.86, 2.33) |
| Maternal education (years) | | | | | |
| <12 | 390 (23.6) | 58 (31.9) | 1.36 (0.94, 1.96) | 29 (31.2) | 1.42 (0.85, 2.36) |
| 12 | 647 (39.2) | 71 (39.0) | Ref | 34 (36.6) | Ref |
| >12 | 543 (32.9) | 44 (24.2) | 1.70 (0.77, 3.75) | 24 (25.8) | 2.66 (1.06, 6.67) |
| Gravidity | | | | | |
| 1 | 340 (20.6) | 28 (15.4) | Ref | 24 (25.8) | Ref |
| 2–3 | 543 (32.9) | 46 (25.3) | 1.03 (0.63, 1.68) | 30 (32.3) | 0.78 (0.45, 1.36) |
| >3 | 263 (15.9) | 35 (19.3) | 1.62 (0.96, 2.73) | 14 (15.1) | 0.75 (0.38, 1.49) |

Frequencies of any spina bifida, isolated spina bifida, and multiple spina bifida, may not total 1652, 182 and 93, respectively, due to missing responses. Unadjusted ORs and 95% CIs were estimated for deceased isolated or multiple spina bifida subjects, in comparison to all subjects with spina bifida that were alive.

CI, confidence interval; OR = odds ratio; n = frequency; Ref = reference.

from other congenital anomalies. In children between 1 and 5 years of age, the main causes of death were pneumonia, meningitis, cardiac issues, and other infectious conditions. One infant was reported to have suffered fetal sequelae associated with maternal urinary tract infection during pregnancy. Cardiac causes contributed in deaths among children aged 6 to 10 and 11 to 15 years. Pneumonia and anoxic brain damage were primary contributors among cases aged 16 to 25 years. Causes of deaths in isolated and multiple CHPS were quite different compared with deaths in spina bifida. Most deaths in children with CHPS were due to sudden infant death syndrome or respiratory distress, or other unknown causes. CHPS deaths in young adulthood were predominantly associated with injuries or accidents (Table 6).

## Discussion

We present our findings from one of the largest studies on mortality in spina bifida spanning nearly 6 million births

**TABLE 4.** *Mortality among Individuals with Isolated Spina Bifida in New York (Birth Years: 1983 to 2006)*

| Age of death (years) | Isolated spina bifida ($n = 182$) | Sex | | Maternal race/ethnicity[a] | | | Hydrocephalus | | Cause of death |
|---|---|---|---|---|---|---|---|---|---|
| | | Female ($n = 90$) | Male ($n = 92$) | White ($n = 88$) | Black ($n = 32$) | Hispanic ($n = 47$) | No ($n = 48$) | Yes ($n = 134$) | Description (frequency of cases) |
| | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | |
| < 1 | 88 (48.4) | 49 (54.4) | 39 (42.4) | 42 (47.7) | 16 (50.0) | 23 (48.9) | 37 (77.1) | 51 (38.1) | Spina bifida with hydrocephalus ($n = 18$) |
| | | | | | | | | | Spina bifida w/o hydrocephalus ($n = 7$) |
| | | | | | | | | | Congenital anomalies ($n = 13$) |
| | | | | | | | | | Prematurity ($n = 6$) |
| | | | | | | | | | Congenital hydrocephalus ($n = 4$) |
| | | | | | | | | | Encephalocele ($n = 3$) |
| 1–5 | 47 (25.8) | 22 (24.4) | 25 (27.2) | 22 (25.0) | 7 (21.9) | 12 (25.5) | 6 (12.5) | 41 (30.6) | Spina bifida with hydrocephalus ($n = 13$) |
| | | | | | | | | | Congenital hydrocephalus ($n = 6$) |
| | | | | | | | | | Bronchopneumonia ($n = 3$) |
| 6–10 | 13 (7.1) | 6 (6.7) | 7 (7.6) | 5 (5.7) | 4 (12.5) | 3 (6.4) | 1 (2.1) | 12 (9.0) | Spina bifida with hydrocephalus ($n = 1$) |
| | | | | | | | | | Spina bifida, unspecified ($n = 1$) |
| | | | | | | | | | Cardiac arrest ($n = 1$) |
| | | | | | | | | | Cardiac dysrhythmia ($n = 1$) |
| | | | | | | | | | Pneumonia ($n = 1$) |
| | | | | | | | | | Extrinsic asthma ($n = 1$) |
| | | | | | | | | | Chronic non-alcoholic liver disease ($n = 1$) |
| | | | | | | | | | Congenital hydrocephalus ($n = 1$) |
| | | | | | | | | | Sepsis ($n = 1$) |
| | | | | | | | | | Holoprosencephaly ($n = 1$) |
| | | | | | | | | | Unknown ($n = 3$) |
| 11–15 | 13 (7.1) | 3 (3.3) | 10 (10.9) | 6 (6.8) | 3 (9.4) | 4 (8.5) | 1 (2.1) | 12 (9.0) | Spina bifida with hydrocephalus ($n = 2$) |
| | | | | | | | | | Spina bifida, unspecified ($n = 2$) |
| | | | | | | | | | Conductive hearing loss ($n = 1$) |
| | | | | | | | | | Obstructive hydrocephalus ($n = 1$) |
| | | | | | | | | | Acute rheumatic heart disease ($n = 1$) |
| | | | | | | | | | Pulmonary embolism/infarction ($n = 1$) |
| | | | | | | | | | Bronchopneumonia ($n = 2$) |

**TABLE 4.** *Continued*

| Age of death (years) | Isolated spina bifida (*n* = 182) | Sex | | Maternal race/ethnicity[a] | | | Hydrocephalus | | Cause of death |
|---|---|---|---|---|---|---|---|---|---|
| | | Female (*n* = 90) | Male (*n* = 92) | White (*n* = 88) | Black (*n* = 32) | Hispanic (*n* = 47) | No (*n* = 48) | Yes (*n* = 134) | Description (frequency of cases) |
| | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | |
| | | | | | | | | | Aplastic anemia (*n* = 2) |
| | | | | | | | | | Wiskott-Aldrich Syndrome (*n* = 1) |
| | | | | | | | | | Unknown (*n* = 1) |
| 16–20 | 7 (3.9) | 4 (4.4) | 3 (3.3) | 3 (3.4) | 1 (3.1) | 3 (6.4) | 0 (0) | 7 (5.2) | Multiple congenital anomalies (*n* = 2) |
| | | | | | | | | | Congenital ichthyosis (*n* = 1) |
| | | | | | | | | | Hypertrophic cardiomyopathy (*n* = 1) |
| | | | | | | | | | Holoprosencephaly (*n* = 1) |
| | | | | | | | | | Arnold-Chiari syndrome (*n* = 1) |
| | | | | | | | | | Chromosomal-mosaicism (*n* = 1) |
| 21–25 | 12 (6.6) | 4 (4.4) | 8 (8.7) | 8 (9.1) | 1 (3.1) | 3 (6.4) | 3 (6.3) | 9 (6.7) | Spina bifida (*n* = 4) |
| | | | | | | | | | Hydrocephalus (*n* = 1) |
| | | | | | | | | | Heart failure (*n* = 1) |
| | | | | | | | | | Urinary Tract Infection (*n* = 1) |
| | | | | | | | | | Injury (*n* = 2) |
| | | | | | | | | | Parasitic infection (*n* = 1) |
| | | | | | | | | | Unknown (*n* = 2) |
| 26–28 | 2 (1.1) | 2 (2.2) | 0 (0) | 2 (2.3) | 0 (0) | 0 (0) | 0 (0) | 2 (1.5) | Malignant neoplasm of bladder (*n* = 1) |
| | | | | | | | | | Acute vascular intestinal disorder (*n*−1) |

[a]Maternal race/ethnicity does not include "Other race/ethnic" groups for age at death groups <1, 1–5, 6–10 years, and hence does not equal the total number of isolated cases in those age groups.

**TABLE 5.** *Mortality among Individuals with Multiple Spina Bifida in New York (Birth Years: 1983 to 2006)*

| Age of death (years) | Isolated spina bifida ($n = 93$) | Sex | | Maternal race/ethnicity[a] | | | Hydrocephalus | | Cause of death |
|---|---|---|---|---|---|---|---|---|---|
| | | Female ($n = 41$) | Male ($n = 52$) | White ($n = 43$) | Black ($n = 18$) | Hispanic ($n = 27$) | No ($n = 32$) | Yes ($n = 61$) | Description (frequency of cases) |
| | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | |
| < 1 | 53 (57.0) | 24 (58.5) | 29 (55.8) | 26 (60.5) | 11 (61.1) | 14 (52.9) | 23 (71.9) | 30 (49.2) | Multiple congenital anomalies ($n = 6$) |
| | | | | | | | | | Congenital lung disorder ($n = 4$) |
| | | | | | | | | | Congenital anomalies of diaphragm ($n = 1$) |
| 1–5 | 24 (25.8) | 8 (19.5) | 16 (30.8) | 8 (18.6) | 4 (22.2) | 9 (33.3) | 5 (15.6) | 19 (31.2) | Spina bifida with hydrocephalus ($n = 1$) |
| | | | | | | | | | Spina bifida w/o hydrocephalus ($n = 1$) |
| | | | | | | | | | Meningitis ($n = 1$) |
| | | | | | | | | | Pneumonia ($n = 2$) |
| | | | | | | | | | Sequelae of chronic liver disease ($n = 1$) |
| | | | | | | | | | Congenital anomalies of brain ($n = 1$) |
| | | | | | | | | | Web of larynx ($n = 1$) |
| | | | | | | | | | Disease of intestine ($n = 1$) |
| | | | | | | | | | Pathological fracture ($n = 1$) |
| | | | | | | | | | Newborn affected by maternal UTI ($n = 1$) |
| | | | | | | | | | Common arterial trunk ($n = 1$) |
| | | | | | | | | | Craniosynostosis ($n = 1$) |
| 6–10 | 9 (9.7) | 3 (7.3) | 6 (11.5) | 3 (7.0) | 2 (11.1) | 4 (14.8) | 4 (12.5) | 5 (8.2) | Spina bifida with hydrocephalus ($n = 2$) |
| | | | | | | | | | Spina bifida unspecified ($n = 1$) |
| | | | | | | | | | Sepsis ($n = 1$) |
| | | | | | | | | | Viral pharyngoconjunctivitis ($n = 1$) |
| | | | | | | | | | Myocardial degeneration ($n = 1$) |
| | | | | | | | | | Cardiac anomaly ($n = 1$) |
| 11–15 | 4 (4.3) | 4 (9.8) | 0 (0) | 4 (9.3) | 0 (0) | 0 (0) | 0 (0) | 4 (6.6) | Spina bifida, unspecified ($n = 1$) |
| | | | | | | | | | Congenital malformation ($n = 1$) |
| 16–20 | 2 (2.2) | 2 (4.9) | 0 (0) | 1 (2.3) | 1 (5.6) | 0 (0) | 0 (0) | 2 (3.3) | Pneumonia ($n = 1$) |
| | | | | | | | | | Non-specific musculoskeletal ($n = 1$) |
| 21–25 | 1 (1.1) | 0 (0) | 1 (1.1) | 1 (2.3) | 0 (0) | 0 (0) | 0 (0) | 1 (1.6) | Anoxic brain damage ($n = 1$) |
| 26–28 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | – |

[a]Maternal race/ethnicity does not include "Other race/ethnic" groups for age at death groups <1, 1–5, 6–10 years, and hence does not equal the total number of isolated cases in those age groups.

in the state of NY. We found that the survival probability in spina bifida is low compared with the comparison group of CHPS cases, at all ages. A majority of the deaths in spina bifida occur in the first year of life; however, a higher risk of death persisted for individuals with spina bifida even at older ages throughout the study follow-up. Most common causes of death in early childhood include those associated with complications of hydrocephalus, sepsis or infections, cardiac complications, pneumonia, pulmonary embolism; and among adults – infections, heart or kidney failure, injuries, and neoplasms contribute to most deaths. Several of these causes, including complications of hydrocephalus, infections, injuries, renal failure in both children and young adults.

In our study, 16.9% of spina bifida cases died by the end of the follow-up period. This rate varied widely in the literature, and is also influenced by factors like study source and design, and length of the follow-up. A majority

**TABLE 6.** *Mortality among Individuals with Isolated and Multiple Congenital Hypertrophic Pyloric Stenosis in New York (Birth Years: 1983 to 2006)*

| | Isolated congenital hypertrophic pyloric stenosis (*N*=70) | | Multiple congenital hypertrophic pyloric stenosis (*N*=32) | |
|---|---|---|---|---|
| **Age of death (years)** | ***n* (%)** | **Causes of death Description (frequency of cases)** | ***n* (%)** | **Cause of death Description (frequency of cases)** |
| <1 | 27 (38.6) | Sudden infant death (*n*=3) | 9 (28.1) | Congenital cardiac malformation (*n*=2) |
| | | Respiratory distress/birth asphyxia (*n*=3) | | Infection (*n*=1) |
| | | Prematurity (*n*=2) | | Volvulus (*n*=1) |
| | | Cardiac causes (*n*=2) | | Neonatal hypertension (*n*=1) |
| | | Pyloric stenosis (*n*=1) | | Respiratory (*n*=1) |
| | | Labor complication (*n*=1) | | Other congenital anomalies (*n*=3) |
| | | Unknown or unspecified (*n*=9) | | |
| | | Other causes (*n*=6) | | |
| 1–5 | 22 (31.4) | Injury (*n*=6) | 15 (46.9) | Anoxic brain damage (*n*=1) |
| | | Sudden death (*n*=2) | | Chromosomal cause (*n*=1) |
| | | Drowning (*n*=1) | | Cardiac causes (*n*=5) |
| | | Assault (*n*=1) | | Pulmonary causes (*n*=3) |
| | | Pneumonia (*n*=2) | | Congenital anomalies (*n*=1) |
| | | Neoplasm (*n*=2) | | Degenerative nervous system (*n*=1) |
| | | Unknown (*n*=1) | | Ill-defined or Unknown cause (*n*=2) |
| | | Other causes (*n*=7) | | Other causes (*n*=1) |
| 6–10 | 5 (7.1) | Injury (*n*=1) | 0 | – |
| | | Poisoning (*n*=1) | | |
| | | Other (*n*=1) | | |
| | | Neoplasm (*n*=1) | | |
| 11–15 | 5 (7.1) | Injury (*n*=2) | 1 (3.1) | Neoplasm (*n*=1) |
| | | Diabetic ketoacidosis (*n*=1) | | |
| | | Neoplasm (*n*=1) | | |
| | | Cardiac complication (*n*=1) | | |
| 16–20 | 3 (4.3) | Assault (*n*=1) | 5 (15.6) | Hepatic failure (*n*=1) |
| | | Injury (*n*=1) | | Malformation of coronary vessels (*n*=1) |
| | | Hanging/suffocation (*n*=1) | | Assault (*n*=1) |
| | | | | Injury (*n*=2) |
| 21–25 | 6 (8.6) | Accidental poisoning (*n*=3) | 1 (3.1) | Accident (*n*=1) |
| | | Assault (*n*=1) | | |
| | | Other Unknown (*n*=2) | | |
| 26–28 | 3 (2.9) | Accident (*n*=1) | 1 (3.1) | Ill-defined or unknown (*n*=1) |
| | | Hanging/suffocation (*n*=2) | | |

of previous studies, using large hospital-based case series, reported a greater percentage of deaths among those affected with spina bifida, compared with our study. Kalucy et al. (1994) in Western Australia reported 52% mortality, while Bowman et al. (2001) reported 23.7% mortality. Recent studies based on a longer follow-up interval and from large referral hospitals reported 30% to 60% deaths among individual affected with spina bifida

(Oakeshott et al., 2010; Roach et al., 2011). The only other study based on a birth defects registry that we found is from the Metropolitan Atlanta Congenital Defects. In birth years 1979 to 1994, with a follow-up period of 18 years, their estimate of deaths in spina bifida cases (45/235) were similar to our findings (336/1988) (19.1% vs. 16.9%, respectively) (Wong and Paulozzi, 2001).

Past studies have found an association between spina bifida survival and infant's sex, age, race and ethnicity, low birth weight, level of the lesion, presence of other birth defects, and birth year (Shin et al., 2012; Wong and Paulozzi, 2001; Wang et al., 2010). Particularly, our finding is consistent with another large study that combined data from 10 population-based birth defects monitoring programs in the United States, including NY, where low birth weight was reported as a strongest predictor for mortality at birth and up to age 8 years, after adjusting for race (Shin et al., 2012). However, we did not find an association between maternal race and ethnicity and the risk of death, as noted in their study (Shin et al., 2012). We were unable to examine the role of level of lesion.

Our study is the first population-based analysis to examine causes of death, by "isolated" and "multiple" spina bifida, in different age strata of affected cases. The only other registry-based study on spina bifida mortality was from the Metropolitan Atlanta Congenital Defects Program, including 235 cases and a follow-up of 18 years reporting 45 deaths; however, this study did not examine specific causes of death. Our findings on causes of death are comparable to other large studies using hospital-based series of spina bifida cases. Oakshott et al. (2010) followed 117 cases of spina bifida from a large referral hospital, with a follow-up of 38 years. They reported 71 deaths during the study period, and a high number of deaths were due to unexpected causes such as epilepsy, pulmonary embolus, acute hydrocephalus, and acute renal sepsis. Furthermore, the survival curves presented in their study, comparing all cases of spina bifida with the general population in UK, closely matches the survival plots in the current study. Data from another referral hospital in Texas, with a 45-year follow-up period, reported the most common causes of death in spina bifida patients were infection, hydrocephalus, heart failure, kidney failure, and other unknown reasons (Roach et al., 2011). A large study from Ireland, with a 40-year follow-up of cases from a referral hospital, reported 18 deaths in a cohort of 280 cases, and reasons for death included renal failure, infection, cardiac failure, postsurgery for Chiari malformation, respiratory arrest, possible shunt malfunction, status epilepticus, myocardial infarction, perforated duodenal ulcer, and ruptured basilary artery aneurism (McDonnell and McCann, 2000).

Cardiac defects were noted in a majority of spina bifida cases with multiple defects. This co-occurrence was also reported in the 10 US registry-based analyses by Shin et al. (2012). It was not possible to assess cause-specific mortality in cases with co-occurring spina bifida and cardiac defects, as we did not have information on treatment methods and complications associated with each of the birth defects. More studies are warranted to examine individual roles of spina bifida and cardiac malformations on mortality.

There are several strengths to our study. By excluding genetic syndromes and those with known etiology from our cause of death analysis, we were able to achieve a homogenous sample of "isolated" and "multiple" cases of spina bifida and CHPS. Subjects were identified using a statewide, population-based surveillance. Including data from both Upstate NY and NYC, not only increased the number of subjects with spina bifida and CHPS, but also improved the representativeness of our study findings across various race and ethnic groups. A limitation of our study was that information from birth records may not always be reliable, and temporal variations in information collected on birth and death certificates. It is possible that we may have missed some deaths due to mismatched linkages, or if deaths occurred outside NY State. However, past studies using National Death Index have found very few additional deaths. We were unable to collect detailed information on the level of lesion, cause of death (in cases where multiple causes are involved), as well as treatment type and complications associated with spina bifida, which may have given us valuable information on potentially important risk factors that contributed to death. Finally, coding errors, and incorrectly reported congenital anomalies to the CMR may introduce bias in our estimates, and hence our findings should be interpreted with some caution.

In conclusion, the increased mortality in spina bifida is a major concern. We found several known causes of death among those with spina bifida. Our findings serve as a reminder to improve clinical care for lethal complications of spina bifida in children and adults living with the defect, and reduce disability and mortality in current and future cases. As more individuals with spina bifida are reaching adulthood, understanding age-specific risks of death and implementation of better screening and treatment strategies for known causes of death is important. Primary prevention of spina bifida is a best approach to prevent unnecessary disability and death associated with the defect in future births. Mandatory folic acid fortification programs in the United States and several other countries have resulted in up to 25% reduction in the occurrence of spina bifida cases globally (MRC Vitamin Study Research Group, 1991; Mosley et al., 2009; Youngblood et al., 2012). Similar primary prevention is urgently needed in countries without fortification policies to reduce the burden of mortality associated with spina bifida.

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