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Characteristics and survival of children with acute leukemia with Down syndrome or other birth defects in New York State

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ABSTRACT

Background: Acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) among DS children have been studied extensively using data from clinical trials or institutional reports. The purpose of this study was to link population-based cancer and birth defects data to evaluate characteristics and survival of children with acute leukemia according to the presence of DS or other birth defects.
Methods: ALL and AML cases diagnosed between 1983 and 2012 among children aged 0-14 years were obtained from the New York State Cancer Registry. Birth defect status (DS, other birth defects, or no birth defects) was determined by linking with birth defects data. Associations between birth defect status and demographic characteristics were evaluated using contingency table analysis. Ten-year survival was calculated by birth defect status and other potential prognostic factors. Cox proportional hazards regression analysis was also performed.
Results: Among 2941 ALL children, 1.6% had DS, 3.8% had other birth defects, and 94.5% had no birth defects. Birth defect status was significantly associated with age at ALL diagnosis. Survivals were similar among three groups. Among 563 AML children, 11.0% had DS, 6.0% had other birth defects, and 83.0% had no birth defects. Children with DS were more likely to be diagnosed with AML at a younger age and showed the best survival.
Conclusion: Age at leukemia diagnosis was significantly associated with the birth defect status. Comparable survival was observed for ALL children. However, AML children with DS demonstrated superior survival compared to children with other birth defects or no birth defects.

1. Introduction

Children with Down syndrome (DS) have a significantly increased risk of developing acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) [1–5]. Leukemia among DS children demonstrates unique clinical and biological characteristics compared to leukemia among non-DS children [6–11]. Even though acute leukemia occurring in DS children has been extensively studied, many of the studies were based on clinical trials or institutional reports. The few investigations that used population-based data were all conducted outside of the United States [12–14]. To the best of our knowledge, no population-based studies have been conducted in the U.S to assess the outcomes of leukemia in DS children. To fill this gap, the current study used cancer data reported to the New York State Cancer Registry (NYSCR) and birth defects data reported to the New York State Congenital Malformations Registry (NYSCMR) to evaluate the characteristics of acute leukemia in DS and non-DS children and compare survival outcomes.

2. Materials and methods

2.1. Source of data

2.1.1. Birth defects data

Birth defects data were obtained from the NYSCMR, which began operations in 1982. As one of the largest statewide population-based birth defects surveillance registries in the nation, the NYSCMR receives more than 12,000 birth defect reports annually [15]. Types of birth defects were coded using the ICD-9-CM diagnosis code (prior to 1992) or the British Pediatric Association (BPA) Classification of Diseases code (1992 and after).

This study included children with a reportable major birth defect (defined by the National Birth Defect Prevention Network [16]) born between 1983 and 2010 in New York. Children were subsequently classified into two larger birth defect groups according to the assigned diagnostic codes: children with DS and children with other birth defects. Some children have multiple birth defects reported to the registry,

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but if DS was listed as one of the defects, they were grouped as children with DS. A file containing child's first name, last name, birth date, sex, Social Security number (when available), address, and certain maternal demographic information was prepared by the NYSCMR and provided to the NYSCR for data linkage and analysis. The study was reviewed and approved by the Institutional Review Board of the New York State Department of Health.

2.1.2. Cancer data

Cancer data reported to the NYSCR were used to select cancer cases for the study. The NYSCR is considered population-based since 1976, and currently registers about 110,000 new invasive cancer cases each year, including about 650 cases diagnosed at age less than 15 years.

This study included ALL and AML cases diagnosed between 1983 and 2012 among children aged 0–14 years. ALL[1] and AML[2] were defined according to the site recode classification provided by the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) [18]. Since the birth defects data only included children born during 1983–2010, we restricted our cancer case selection to the same birth year range. In addition, children born in other states or countries were excluded from the study to be consistent with the birth defects data.

2.1.3. Determination of birth defect status for cancer cases

The birth defect status for children with a leukemia diagnosis was determined by linking leukemia cases with the birth defects data using LinkPlus software [19]. LinkPlus employs probabilistic matching algorithms and assigns scores indicating the likelihood of matches. Personal identifiers, including first name, last name, birth date, sex, and Social Security number (when available) were used for matching. We manually reviewed uncertain matches by using additional information available, such as address. If a child with DS in the birth defects file was matched to a leukemia case, the child was assigned to the group of leukemia with DS; if a child with other birth defects was matched to a leukemia case, the child was assigned to the group of leukemia with other birth defects; if a child in the leukemia case file did not match to a child in the birth defects file, the child was assigned to the group of leukemia with no birth defect.

2.1.4. Univariate data analysis

ALL and AML are two types of leukemia with distinctive characteristics, therefore, all data analyses were performed separately for ALL and AML. Contingency table analyses were conducted for leukemia cases to evaluate the associations between birth defect status and demographic characteristics, including age at cancer diagnosis (< 1, 1–4, 5–9, 10–14), sex, race (white, black, other, unknown), Hispanic ethnicity (Hispanic or non-Hispanic), year of diagnosis (1983–1992, 1993–2002, 2003–2012), vital status (alive or dead), and underlying cause of death (leukemia or non-leukemia). Chi-square statistics were used to test the significance of associations. However, if the expected value in any cell of a contingency table was less than 5, Fisher's exact test was used. SAS v9.3 was used to perform all statistical analyses, and statistical significance was determined based on a 2-tailed p value < 0.05.

2.1.5. Survival analysis

The NYSCR routinely matches cancer cases with New York State death certificates and the National Death Index (NDI) to update vital status and obtain death information (including death date and cause of death) for deceased patients. In the current study, the presumed alive method [20,21] was used to measure survival time, which was computed as the time interval (in months) between cancer diagnosis and death or the end of the study (December 31, 2012). Cases reported only through the death certificate (n = 8) or cases alive with no survival time (n = 9) were excluded from analyses. Ten-year overall survival was calculated by birth defect status for ALL and AML, respectively, using the actuarial method. Survival was also evaluated by other potential prognostic factors, including age, sex, race, ethnicity, and year of diagnosis. The log-rank test was used to compare survival differences among groups. We also performed Cox proportional hazards regression analysis to assess the effect of birth defect status on survival, simultaneously adjusting for confounding variables. The model assumption of proportional hazards was examined.

3. Results

A total of 2,941 ALL and 563 AML cases were included in this study. Among ALL cases, 48 (1.6%) children had DS, 113 (3.8%) children had other birth defects, and 2780 (94.5%) children had no birth defect. Among AML cases, 62 (11.0%) children had DS, 34 (6.0%) children had other birth defects, and 467 (83.0%) children had no birth defect.

Patient demographic information by type of leukemia and birth defect status is displayed in Table 1. For children diagnosed with ALL, birth defect status was significantly associated with age at cancer diagnosis ($P < 0.0001$), with the most notable difference occurring for children of a younger age: 14.2% of ALL were diagnosed during infancy (< 1 year old) for children with other birth defects, compared to 3.1% for children with no birth defect. None of the children with DS was diagnosed within one year of age. However, age distributions were similar across the three birth defect status groups for ALL occurring in the older age groups (5–9, 10–14). No significant associations were observed between birth defect status and the other demographic characteristics evaluated. Birth defect status was also significantly associated with age at cancer diagnosis for AML cases ($P < 0.0001$). However, unlike ALL, AML cases tended to be diagnosed at a much younger age among children with DS. For DS children, our data showed that about 29% of AML cases were diagnosed within the first year of life and all but one AML diagnosis (98.4%) occurred within 5 years of age. AML occurring among children with other birth defects also tended to present at a younger age. Among AML-DS children, 79.0% were still alive by the end of the study; however, only 59.7% were alive among AML children with no birth defect and 47.1% among AML children with other birth defects. AML-DS children were more likely to die from non-leukemia causes (30.8%), compared to 22.2% for AML children with other birth defects and 6.4% for AML children with no birth defect. As with ALL cases, no significant differences were observed for AML cases with regard to sex, race, ethnicity, or year of diagnosis among the three groups for AML cases.

Ten-year survival functions for children diagnosed with ALL or AML by birth defect status are illustrated in Figs. 1 and 2. Overall, 10-year survival rates for ALL were considerably high, ranging from 81.5% for children with DS to 86.1% for children with no birth defect (Fig. 1). The log-rank test showed no significant survival differences among the three groups ($p = 0.691$). For AML children (Fig. 2), those with DS showed the highest survival rate (79.3%), followed by children with no birth

[1] ALL classification included ICD-O-3 histology codes of 9826, 9835-9837, 9811-9818, with a behavior code of 3 (malignant). Histology codes 9811-9818 were added to the 2008 *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues* [17], and were implemented by central cancer registries in the U.S. for cases diagnosed in 2010 and after. For histology codes 9811-9818 to be categorized as ALL, the primary site had to be C420, C421, or C424.

[2] AML classification included the ICD-O-3 histology codes of 9840, 9861, 9865-9867, 9869, 9871-9874, 9895-9898, 9910-9911, 9920, with a behavior code of 3. Histology codes 9865, 9869, 9898, 9911 were added to the 2008 *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues* [17], and were implemented by central cancer registries in the U.S for cases diagnosed in 2010 and after. Transient myeloproliferative disorder (TMD) has a behavior code of 1 (borderline), which is not a reportable condition in the U.S.; and therefore, was not included in the current study. However, if TMD evolved to leukemia, the cases were included in the study because leukemia is a reportable condition.