Cancer Causes and Control, 1996, 7, pp. 411-414

Childhood leukemia following phototherapy for neonatal hyperbilirubinemia (Denmark)

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(Received 2 October 1995; accepted in revised form 7 March 1996)

To test the hypothesis that exposure to high intensity lightning (around 400 nanometers) in neonatal nurseries increases the incidence of childhood leukemia, over 55,120 newborn children treated with phototherapy for hyperbilirubinemia were identified from the Danish Hospital Discharge Register for 1977-89. Linkage of the roster with the national cancer registry through 1991 revealed 87 childhood cancers, whereas 85 were expected from the rates for the general population. The incidence of leukemia in 34 children was not unusual (standardized incidence ratio [SIR] = 1.2, 95 percent confidence interval [CI] = 0.8-1.7). Subgroup analyses revealed no remarkable patterns for any category of leukemia subtype, gender, or age at diagnosis. We conclude that whole-body exposure to phototherapy (420-470 nm) shortly after birth is not a significant risk factor for childhood leukemia. *Cancer Causes and Control*, 1996, 7, 411-414

Key words: Childhood leukemia, Denmark, neonatal hyperbilirubinemia, phototherapy.

Introduction

It has been hypothesized that exposure to fluorescent light lamps and other light sources with strong illumination around 400 nanometers at birth may be related causally to the peak of childhood lymphocytic leukemia (ALL) seen at ages three to four in Caucasian populations.[1] The proposed mechanism is that exposure of protoporphyrins in circulating lymphoblasts of neonates to fluorescent light may generate singlet oxygen[2] or free radicals,[3] which can react with cellular DNA and cause single- and double-strand breaks.[2,4] Because of a significant increase over time in the intensity of fluorescent lighting in both intensive care and term nurseries, it has been suggested that such exposures to 'photosensitizing lighting immediately after birth'[1] may be responsible for the steady increase in the incidence of ALL seen in the United States during the past two decades.[5] The rationale for this hypothesis, however, was questioned by Miller,[6] who pointed out that the rate of childhood leukemia overall was not increasing in the US. The apparent rise in ALL was probably the result of improved diagnoses and/or improved reporting, since the rate of leukemia not-otherwise-specified (NOS) steadily declined over the same calendar years. This same pattern also was observed in Denmark for childhood leukemia, *i.e.*, while ALL increased over time, 'leukemia, NOS' decreased, and there was no change in overall leukemia rates.[7]

The hypothesis predicts that children treated for neonatal hyperbilirubinemia with phototherapy, at 420

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to 470 nm, are at increased risk of ALL. Support for this assumption came from a Dutch study,[8] which reported a higher frequency of phototherapy among 519 children (1.3 percent) with ALL than among 507 control children (0.2 percent). However, the total number of exposed children was small (n = 8) and the difference in exposure frequency was not statistically significant.

We examined the incidence of ALL and other cancers in a large population-based cohort of 55,120 mature neonates with hyperbilirubinemia, who were treated with phototherapy.

Materials and methods

The Danish Central Hospital Discharge Register was used to identify 66,430 neonates who were discharged with a record of neonatal hyperbilirubinemia between 1977 and 1989. During the same period, about 734,500 children were born in Denmark, indicating that about nine percent of all newborns received phototherapy. In addition to the personal identification number unique to every Danish citizen, the Discharge Register contains information on dates of admission and discharge, the hospital department attended, and up to 20 discharge diagnoses on patients admitted to a nonpsychiatric hospital in Denmark since 1977. Hospital discharge diagnoses were classified according to a modified version of the *International Classification of Diseases, Eighth Revision* (ICD-8).[9]

Of the 64,430 children with neonatal hyperbilirubinemia (ICD-8 code 778.91), 10,384 (16 percent) had a supplementary diagnosis of neonatal immaturity (ICD-8 code 777.99); they were excluded from this study to avoid any possible confounding related to factors associated with immaturity *per se*. Another 926 newborns (one percent) notified with hemolytic disease (ICD-8 code for main groups 774 and 775) were also excluded, leaving 55,120 mature children with hyperbilirubinemia for evaluation (Table 1). During the study period (1977-89), 85 to 90 percent of children in Denmark with hyperbilirubinemia were treated with prolonged irradiation with light at wavelengths of 420-470 nm, which stimulates the isomerization of bilirubin and facilitates excretion of the toxic compound. This estimate was based on a random sample of 150 neonates notified in the Hospital Discharge Register with hyperbilirubinemia diagnosed during 1980-81 at one of three different hospital departments: a specialized neonatal unit in Copenhagen (50 children); an obstetrics department from the outer Copenhagen area (50 children); and a pediatrics department in a provincial town (50 children). The medical files of five patients (three percent) were missing; 126 (87 percent) of the remaining 145 newborns had received phototherapy, which was given for an average of 71 hours (range, 24-188 h). Most phototherapy (76 percent) was given for two to four days; 11 percent received phototherapy for less than two days, and 13 percent for more than four days.

Table 1. Descriptive characteristics of mature newborns hospitalized for uncomplicated hyperbilirubinemia, 1977-89, all of Denmark

Characteristic	Number	Person-years through 1991
Entire study group	55,120	499,502
Boys	32,682	295,169
Girls	22,438	204,333
Year of birth		
1977-78	9,857	136,488
1979-80	10,933	130,181
1981-82	9,383	93,062
1983-84	8,032	63,739
1985-86	7,145	42,248
1987-88	6,626	26,075
1989	3,145	7,709
Age during follow-up (yrs)		
0-1		106,492
2-5		193,541
6-14		199,469

The study cohort was linked to the files of the Danish Cancer Registry, which began collecting data on cancer incidence, including childhood leukemia, in 1943.[10] The epidemiologic characteristics of childhood cancer in Denmark since 1943 and an evaluation of the completeness of nationwide registration of this particular age group (over 95 percent) have been given in earlier publications.[7,11] The period of follow-up for cancer occurrence, benign brain tumors included, was taken from the date of discharge for hyperbilirubinemia until the date of death (obtained from the national mortality files) or 31 December 1991. Cancers were classified according to the *International Classification of Diseases, Seventh Revision* (ICD-7).[12] The expected numbers of cancers were calculated by multiplying age-, gender-, and period-specific national incidence rates by the corresponding person-years of the cohort. Tests of significance and confidence intervals for the standardized incidence ratio (SIR), taken as the ratio of observed to expected cancers, were calculated using the exact methods of Miettinen when the observed number of cases were small; otherwise, an accurate asymptotic approximation was used.[13]

Results

For the 55,120 mature neonates with hyperbilirubinemia, 499,502 person-years of follow-up were accrued (Table 1), on average 9.1 years (range, 0-15 years). Overall, 87 cancers were observed, and 85.0 were expected, yielding an SIR of 1.0 (Table 2), 1.1 for boys and 0.9 for girls.

Table 2. Observed (Obs) and expected (Exp) numbers of cases of cancer among 55,120 children with neonatal hyperbilirubinemia in Denmark, 1977-89

Site	Obs	Exp	SIR[a]	CI[b]
All malignant neoplasms	87	85.0	1.0	(0.8-1.3)
Digestive organs	4	2.4	1.7	(0.5-4.3)
Kidney	6	6.0	1.0	(0.4-2.2)
Urinary bladder	2	0.7	3.0	(0.3-11)
Skin	0	1.0	0.0	(0.0-2.9)
Eye	3	4.3	0.7	(0.1-2.0)
Brain and nervous system	25	27.1	0.9	(0.6-1.4)
Thyroid and other endocrine glands[c]	2	2.4	0.8	(0.1-2.8)
Bone	1	1.7	0.6	(0.0-3.4)
Connective tissue	2	1.4	1.5	(0.2-5.3)
Non-Hodgkin's lymphoma	6	4.3	1.4	(0.5-3.0)
Hodgkin's disease	1	1.3	0.7	(0.0-4.1)
Leukemia	34	28.3	1.2	(0.8-1.7)
Other and unspecified sites[d]	1	4.1	0.2	(0.0-1.2)

[a] SIR = standardized incidence ratio.
[b] CI = 95% confidence interval.
[c] One neuroblastoma and one ganglioneuroblastoma of the suprarenal gland.
[d] One ganglioneuroblastoma of the thorax, NOS.

Table 3. Observed (Obs) and expected (Exp) cases of leukemia among 55,120 children with neonatal hyperbilirubinemia by subtype of leukemia, gender, and age during follow-up

	Obs	Exp	SIR[a]	CI[b]
Acute lymphatic leukemia (ALL)	28	24.6	1.1	(0.8-1.7)
Gender				
Boys	17	15.9	1.1	(0.6-1.7)
Girls	11	8.7	1.3	(0.6-2.3)
Age during follow-up (yrs)				
0-1	5	3.0	1.7	(0.6-3.7)
2-5	18	16.6	1.1	(0.7-1.7)
6-14	5	5.0	1.0	(0.4-2.2)
Non-ALL subtypes	6	3.8	1.6	(0.6-3.3)
Gender				
Boys	3	1.9	1.6	(0.4-4.3)
Girls	3	1.9	1.6	(0.4-4.4)

[a] SIR = standardized incidence ratio.
[b] CI = 95% confidence interval.

Leukemia was the most frequent malignancy, with a total of 34 cases observed and 28.3 expected (SIR = 1.2, 95 percent confidence interval [CI] = 0.8-1.7), 1.1 for boys and 1.3 for girls. Brain cancer was observed at the next highest frequency, with 25 cases, but at a lower incidence than expected (SIR = 0.9). No childhood cancer occurred at a rate significantly different from that expected.

The risk for leukemia was examined by histologic type, gender, and age at occurrence (Table 3). No remarkable pattern was seen and there were no significant findings in any of the subgroup analyses. Most of the cases of childhood leukemia were ALL, with 28 observed and 24.6 expected. The risk was similar for girls (SIR = 1.3, $n = 11$) and boys (SIR = 1.1, $n = 17$). Table 3 also shows the SIR for ALL in three age groups of childhood defined *a priori*. Most of the cases occurred two to five years after birth, but the risk was not significantly increased (SIR = 1.1, $n = 18$). Only six cases of non-ALL occurred, with 3.8 expected.

Discussion

Many analytic studies have attempted to elucidate the cause of the distinct peak of childhood ALL at ages three

to four seen in all the surveyed populations of Caucasian origin, and to varying extents in other populations.[14] An incidence peak that appears so early in life suggests that the leukemogenic event may occur during fetal life or near the time of birth; however, no generally accepted explanations for the peak have been identified. Recently, it was suggested that fluorescent lamps and other light sources with strong illumination of about 400 nm have the capacity to induce malignant transformation of protoporphyrin-loaded lymphoblasts in neonates,[1] and this suggestion seemed to be supported by the results of a small case-control study from the Netherlands showing a relationship between phototherapy (420 to 470 nm) for neonatal hyperbilirubinemia and childhood ALL.[8]

Our large series of over 55,000 newborn children of whom 85 to 90 percent were exposed to intense light during treatment for hyperbilirubinemia revealed no increase in childhood leukemia or other childhood cancers. While it is difficult to prove a negative, our study was sufficiently precise as to exclude (with 95 percent confidence) an excess relative risk of 1.7 for leukemia and 1.3 for all cancers. There were no significant findings in any of the subgroup analyses of leukemia type, gender, or age at diagnosis to suggest that phototherapy was related to childhood leukemia. Because information on duration of treatment was not readily available for cohort members, other than for the sample of 145 children, we were unable to evaluate the existence of a dose-response relationship between phototherapy and leukemia. Nonetheless, children treated for hyperbilirubinemia received substantially higher exposures to fluorescent light (420 to 470 nm) than do newborns exposed to the general lighting of intensive care and term nurseries, which formed the basis for the hypothesis generated by Ben-Sasson *et al.*[1] Since a leukemia-effect overall was not apparent at these intense therapeutic exposure levels, it seems unlikely that the much lower levels found in nurseries would be hazardous.

Children with hyperbilirubinemia were identified from the Hospital Discharge Register prior to the registration of the cancer outcome, so that any bias caused by selection of study subjects is unlikely. Our study was population-based, and the cases were identified from a high-quality national cancer registry, with little evidence for under-reporting. Our finding of no significant association between phototherapy and childhood leukemia is supported further by descriptive data on the incidence of childhood leukemia in the national population of Denmark since 1943. While phototherapy for neonatal hyperbilirubinemia was introduced during the 1960s and became common during the 1970s and 1980s (about nine percent of all newborns treated), the incidence of leukemia has remained unchanged, at approximately 44 new cases per one million children per year.[7] The frequency of phototherapy in neonates today is about five percent.

Although the hypothesis is intriguing, we conclude that phototherapy and associated exposure to strong illumination of newborns is not a significant risk factor for childhood leukemia.

Acknowledgements—We thank Drs S. Petersen, Neonatal Unit, the National University Hospital; P. I. Jørgensen, Department of Obstetrics, Herlev Hospital; and N. C. Christensen, Department of Pediatrics, Sønderborg Hospital for help in assessing the frequency of phototherapy in neonatal hyperbilitubinemia.

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