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Florence Menegaux[1,2], Andrew F. Olshan[1], Joseph P. Neglia[3] Brad H. Pollock[4], Melissa L. Bondy[5]

Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC.

[2] Institut National de la Santé et de la Recherche Médicale, INSERM U170-IFR69, 94800 Villejuif, France.

[3] Department of Pediatrics, University of Minnesota, Minneapolis, MN

[4] Center for Epidemiology and Biostatistics, University of Texas Health Science Center at San Antonio, San Antonio, TX.

[5] Department of Epidemiology, MD Anderson Cancer Center, University of Texas, Houston, TX.

Correspondence to:

Andrew F. Olshan, PhD
Children's Oncology Group
P.O. Box 60012
Arcadia, CA 91066-6012
Ph: (626) 447-0064×228
Fax: (626) 445-4334
Email: andy_olshan@unc.edu
Cc: smason@childrensoncologygroup.org

Running head: Day Care, Childhood Infection, Allergy and Neuroblastoma.

Abstract Word Count: 182

Text Word Count: 2,383

This is a pre-copy-editing, author-produced PDF of an article accepted for publication in American Journal of Epidemiology following peer review. The definitive publisher-authenticated version Am J Epidemiol 2004; 159:843-851. is available online at: http://aje.oxfordjournals.org/cgi/content/full/159/9/843.

ABSTRACT

Neuroblastoma is the most common cancer in infants worldwide but little is known about its etiology. Infectious etiologies involving the immune system have been hypothesized for some childhood cancers, especially leukemia, but the role of infectious agents in neuroblastoma has not been fully investigated. We used data from a large case-control study conducted by the Children's Oncology Group over the period 1992-1994 in United States or Canada to investigate if there was any relation between day care attendance, childhood infections, allergies and neuroblastoma. We interviewed mothers of 538 case and 504 age-matched control children by telephone about several factors including pregnancy, medical history, lifestyle, and childhood medical conditions and exposures. Our results suggested decreased risks associated with day care attendance (odds ratio (OR) = 0.81; 95% confidence interval ([CI]: 0.56-1.17), childhood infectious diseases (chickenpox, mumps, red and German measles) (OR = 0.60;CI: 0.39-0.93) and allergies (OR = 0.68; CI: 0.44-1.07). We found reduced neuroblastoma risk associated with markers of potential childhood infections, which suggests a possible role of infectious agents in neuroblastoma etiology. Future epidemiologic studies should incorporate more direct infection data.

Keywords: Neuroblastoma; Day Care; Infection; Allergy; Childhood

Neuroblastoma is an embryonal malignancy of the sympathetic nervous system that derives from primordial neural crest cells. It is the third most common cancer in children and the most common tumor in infants (1). In an analysis of United States Surveillance Epidemiologic End Results (SEER) incidence data, 41 percent of infant neuroblastomas were diagnosed during the first 3 months of life (2). Little is known about the etiology of neuroblastoma and the relatively young age at onset has led researchers to investigate parental factors before conception or during gestation. These factors have included occupation, smoking and alcohol consumption, medication use during pregnancy, pregnancy history, and birth characteristics (3). Associations between these factors and neuroblastoma risk have been inconsistent (2, 3).

Infections are suspected to play a role in the etiology of some childhood cancers, especially childhood acute leukemia and Hodgkin disease (4-6). Kinlen postulated that childhood leukemia is a rare response to a specific infection, and the risk of infection increases through the mixing of populations (7-9). Greaves hypothesized that childhood leukemia may result from a two-step process, with a first step possibly an in utero mutation in a small population of cells. The second step, a postnatal event, may be an additional mutation or proliferation of the initially mutated cell population. It has been suggested that the second event may result from exposure to an infectious agent. By contributing to the normal maturation of the immune system and the establishment of immunocompetence, early common infections or factors that favor infections in early childhood would protect the child against leukemia, while relative isolation would make the child more vulnerable (10, 11). In fact, several studies observed that the risk of childhood leukemia might be reduced by day care attendance (12-14), breast-feeding (6, 13, 15-19), early common infections (14, 20, 21), or population mixing (22-26). Moreover, a recent analysis of data from the present neuroblastoma study found a reduced odds ratio for breast-feeding (27). In this context,

factors that influence children's immune systems are of special interest. To our knowledge, the relationship between neuroblastoma and factors related to the immune system have never been investigated fully. This paper focuses on markers of childhood infections and immune response, including day care attendance, birth order, childhood infections and allergies in relation to neuroblastoma.

MATERIALS AND METHODS

Study population

Details of this study have been published elsewhere (28). Cases were children and young adults under 19 years old who were newly diagnosed with neuroblastoma between May 1, 1992 and April 30, 1994 at any of 139 participating hospitals in the United States and English-speaking Canada. The hospitals were members of one of two collaborative pediatric clinical trials groups, the Children's Cancer Group and the Pediatric Oncology Group (29). The two groups merged to form the Children's Oncology Group. Treating physicians gave us permission to approach parents of patients about participation in the study. Criteria for inclusion of eligible cases were availability of the biological mother for interview, a telephone in the home, and the ability of the mother to speak English or Spanish. Among 741 potentially eligible cases, 538 (73 percent) case mothers were interviewed successfully. Reasons for nonparticipation of mothers included physician refusal (n=90; 12 percent) mother's refusal (n=57; eight percent), not traceable (n=44; six percent) ,and other reasons (n=12; two percent).

One control was selected for each case using a random-digit dialing method based on the first eight digits of the case's telephone number (30). Controls were individually matched to cases by telephone number and on the date of birth (within 6 months older or younger for cases diagnosed at younger than 3 years old, within 1 year older or younger for cases over 3

years old). The parents of cases and controls were interviewed about exposures and events prior to a common reference date: the case date of diagnosis. The household random-digit dialing screening response proportion was 74 percent (31). Among 703 eligible control mothers, 504 (72 percent) completed interviews.

Data collection

Mothers of cases and controls were contacted after signed consent forms were received from responsible physicians. After initial contact, parents were sent packets that contained consent forms and interview guides to facilitate recall and increase interview efficiency. Parents' telephone interviews were conducted by trained interviewers. Parents of cases and controls were asked about demographic characteristics, occupational history, pregnancy history and birth characteristics, medication use, children's illnesses and conditions, lifestyle, and other factors. Data related to infections and factors potentially promoting infections included history of day-care attendance, birth order of index children, history of selected childhood infections, history of ear infections, history of other infections. History of children's illnesses and conditions also were collected by maternal self-report. Day-care variables included day care (ever/never), age at starting day care, age at ending day care, and number of hours per week. Selected childhood infections included chickenpox, mumps, red measles, and German measles. Mothers were asked to report conditions diagnosed by physicians. Other conditions of interest were disorders such as asthma, hay fever, eczema, and other allergies (ear throat nose allergy as rinitis and sinusitis, dermatological allergy as urticaria, contact dermatitis, food dermatitis and hypersensitivity to drugs).

Statistical analysis

All analyses were performed using the SAS computer software (version 8.1, Cary, North Carolina). The odds ratio (OR) and 95% confidence interval (CI) were estimated using

unconditional logistic regression. The original matching factor, reference age at diagnosis, was taken into account in the unmatched analyses using a six-level categorical variable (< 1 year, 1-2 years, 3-4 years, 5-6 years, 7-10 years, ≥ 11 years). Mothers' demographic characteristics such as educational level (<high school, high school, college), maternal race/ethnicity (white, black, Hispanic, other) and mothers' report of annual total household income in birth year (<$10,000, $10-20,000, $21-30,000, $31-40000, $41-50,000 >$50,000) also were included in analyses as potential confounders. Conditional logistic regression using the 504 matched pairs did not differ materially from the unconditional logistic regression analyses. Day care was defined as day care attendance outside the home. We used four different variables: a dichotomous variable (ever/never), age child started day care, day-care duration, and total hours day care exposure which combined day care duration and number of hours attended per week. We analyzed the day care measures excluding the year before diagnosis to eliminate the potential of the disease to affect day care utilization. The year before diagnosis has been excluded for both cases and controls, the year before diagnosis for controls is the year before the reference date. Childhood infections and allergies were analyzed in children older than 1 year. We included 538 cases and 504 controls in the analysis.

RESULTS

Among case children, 38 percent were less than 1 year old at diagnosis, 35 percent were 1 to 2 years of age, 17 percent 3 to 4 years, and 10 percent were 5 years old or more. Slight case-control differences were found for gender, maternal race, and maternal age at birth (table 1). More case mothers than control mothers had low educations (OR < high school vs. college= 1.4; CI = 0.9-2.2). The proportion of cases from lower-income households (< $

10,000 annually) and higher-income households (> $ 50,000 annually) were higher than among controls.

Twenty-two percent of cases and 28 percent of controls ever attended day care (OR = 0.81; 95 percent CI = 0.56-1.17) (table 2). Day care duration of 6 months or more and total hours day care exposure of 500 hours or more suggested a decreased risk for neuroblastoma (OR = 0.75; 95 percent CI = 0.52-1.10; OR = 0.74, 95 percent CI = 0.51-1.09; respectively). Our results were more pronounced when the year before diagnosis was not excluded: OR = 0.74; 95 percent CI = 0.55-0.99 for day care ever/never, OR = 0.66; 95 percent CI = 0.48-0.90 for day care duration of 6 months or more, and OR = 0.65; 95 percent CI = 0.47-0.89 for total hours day care exposure of 500 hours or more. The analyses were adjusted for child's diagnosis reference age, household income and mother's education, all results remained unchanged after adjustment.

We found strong inverse association in children who were breast-fed and ever attended day care, with an OR of 0.46 (95 percent CI = 0.28-0.74) while ORs were 0.71 (95 percent CI = 0.48-1.04) and 0.85 (95 percent CI = 0.48-1.52), respectively for children who were breast-fed only and children who ever attended day care only. Moreover, an OR of 0.36 (95 percent CI = 0.16-0.81) for children who attended day care 6 months or more and children who were breast-fed more than 6 months was observed (table 4). We did not find any association between birth order and neuroblastoma (OR for three or more siblings compared with one sibling = 0.94, 95 percent CI = 0.67-1.31).

We found an inverse association between any selected childhood infections (chickenpox, mumps, German measles, and red measles) and neuroblastoma (OR = 0.60; 95 percent CI = 0.39-0.93) (table 3). The association was stronger for children who had two or

more infectious diseases (OR = 0.13; 95 percent CI = 0.02-0.65), although the result is based on small numbers. Ear infections were associated with elevated odds ratios (OR = 1.76; 95 percent CI = 1.20-2.58). Decreased risk was found for history of hay fever, asthma, or any allergy (OR = 0.43; 95 percent CI = 0.18-1.04; OR = 0.69; 95 percent CI = 0.36-1.34; OR = 0.68; 95 percent CI = 0.44-1.07, respectively). There was a general pattern of lower risks for day care and breast-feeding with ear infections and other infections but not with infantile disease (table 4).

DISCUSSION

Our results suggest that day care attendance, selected childhood infections, and certain allergic disorders were associated with a reduced risk of neuroblastoma, although odds ratios for ear infection and other infections were elevated. The strengths of our study included a large sample, a detailed interview-administered questionnaire, and extensive collection of covariate information. However, our results should be considered in light of potential study limitations.

Response proportions in case and control groups were below 75 percent, which might indicate selection bias. We did not have direct information to characterize nonrespondents. Potential differences in the response proportions among mothers of cases and controls can result in socioeconomic-related differences. Day care attendance is more common among children of women with higher educations and incomes. Control mothers who participated in this study had slightly higher educations and household incomes than cases. The results remained unchanged after adjustment for these socioeconomic factors, but we cannot rule out the possibility that residual confounding by socioeconomic status or other unmeasured characteristics associated with participation among controls influenced our results.

Another concern is maternal recall, especially differential recall patterns. Maternal recall bias related to day care information seems unlikely, recall of childhood diseases and infections may have led to misclassification. Ten years ago, a British study investigated mother's reports of childhood infections and their concordance with general practitioner records. Questions of two types were asked about infections : closed-ended questions were used for specific childhood infections as chickenpox, mumps, red measles, and German measles, and open-ended questions were asked for other infections. Specific childhood infections were systematically reported more often by mothers compared with general practitioners' records. Mother's reports might be considered the preferred data source for these specific infections that often do not require consultation with a physician. However, for report of other infections obtained by open-ended questions, the accuracy of mothers' recall was poor. In our study, questions about infections were asked with closed-ended questions for specific infections (chickenpox, mumps, red and German measles, and ear infections) and open-ended questions for other infections. Thus, with respect to misclassification, we could consider our results concerning specific infections as more valid than results for other infections. Another potential bias is that the cases' diseases might have reduced their day care attendance . We excluded the year before diagnosis to minimize potential for this bias.

To our knowledge this was the first study to evaluate the effect of markers of childhood infections and immune responses on risk of neuroblastoma. A recent analysis of data from the present neuroblastoma study found reduced ORs for children who breast-fed (27) and encouraged us to investigate the leukemia "infectious hypothesis" for neuroblastoma. Interestingly, we found a decreased risk of neuroblastoma for children who attended day care. Some recent studies of childhood acute leukemia found similar inverse association with

breast-feeding (6, 13, 15-19) and day care (12-14). Day care and breastfeeding together further reduced the risk of neuroblastoma. Some of the infection and breastfeeding results indicated a reduced risk but were based on a small number of subjects. Our previous analysis of breastfeeding and neuroblastoma found a pattern of reduced risk with breastfeeding (27). The results of this study and the earlier report suggest that breastfeeding in combination with other factors deserves further investigation.

We observed reduced ORs for the usual childhood infectious diseases (chickenpox, mumps, German and red measles), that have never been investigated before in relation to neuroblastoma. Results on association between conditions such as chickenpox, measles, rubella, mumps, and childhood leukemia have been mixed (14, 15, 20, 21, 32, 33). Allergic disorders also were of interest because they involve challenges to the immune system. We observed reduced OR with hay fever and asthma. An inverse association between allergies and neuroblastoma also was found by Schuz et al. (34).

The biologic mechanisms that explain our findings are unclear at present. An infectious etiology or immunologic modifiers for neuroblastoma development have not been prominent hypotheses. Nonetheless, there are several lines of laboratory research that provide some clues. There has been significant interest in the mechanisms responsible for high spontaneous regression rate of neuroblastoma (the second highest of any human cancer). One possible mechanism involves immunologic factors and recent studies have reported that the presence of natural immunoglobulin (Ig)M antibodies was cytotoxic for human neuroblastoma cells *in vitro* and *in vivo* (35, 36). Another relevant research area involves investigation of viral etiology. A recent study suggested that the BK polyomavirus was associated with

neuroblastoma. The virus is a relatively common childhood infection without symptoms, but latent or persistent infections may become reactivated. The study found BK virus DNA in the tumor cells of 17 of 18 neuroblastomas, but not in any of five normal adrenal medullas (37). Another common early childhood polyomavirus, the human neurotrophic JC virus, has been associated with pediatric medulloblastomas (38, 39). Although far from definitive, these disparate findings suggest that infectious agents and immune response may influence the risk of pediatric solid tumors.

Future epidemiologic studies should incorporate more direct measures of infection. Additional laboratory studies that evaluate immunologic influences on the development, progression, and regression of neuroblastoma also are warranted.

ACKNOWLEDGMENTS

This study was supported in part by grant CA57004 from the National Cancer Institute. Contributing Children's Cancer Group and Pediatric Oncology Group investigators, institutions, and grant numbers are given in the Appendix. This work was also supported by the Association pour la Recherche contre le Cancer (ARC) and in part by a grant from the National Institute of Environmental Health Sciences (P30ES10126). We wish to thank Drs. David Savitz and Charles Poole for their advice and Drs. Julie Ross and Les Robison for helpful comments on an earlier draft.

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TABLE 1. Demographic characteristics

	Cases		Controls		OR*	95% CI†
	N°	%	N°	%		
Gender						
Male	301	56	251	50	1.0	reference
Female	237	44	253	50	0.8	0.6-1.0
Mother's age at birth (years)						
< 20	48	9	35	7	1.3	0.8-2.1
20-24	119	22	110	22	1.1	0.8-1.5
25-30	212	39	206	41	1.0	reference
31-39	148	28	146	29	1.0	0.7-1.3
40 +	11	2	7	1	1.5	0.6-3.9
Mother's race						
White	429	80	396	79	1.0	reference
Black	42	8	39	8	1.0	0.6-1.6
Hispanic	49	9	54	11	0.8	0.5-1.2
Other	18	3	15	3	1.1	0.5-2.2
Mother's education						
< High school	60	11	51	10	1.4	0.9-2.2
High school	366	68	318	63	1.4	1.0-1.9
College	112	21	135	27	1.0	reference
Household income in birth year‡						
< $ 10 k	89	18	54	11	2.2	1.4-3.4
$ 10-20 k	92	18	91	19	1.3	0.9-2.0
$ 21-30 k	87	17	114	23	1.0	reference
$ 31-40 k	79	16	86	18	1.2	0.8-1.9
$ 41-50 k	54	11	52	11	1.4	0.9-2.2
> $ 50 k	107	21	89	18	1.6	1.1-2.4

* Unmatched odds ratio (OR) adjusted for child's diagnosis reference age.

† CI: confidence interval.

‡ A total of 30 case and 18 control subjects had missing income data.

TABLE 2. Day care attendance and risk of neuroblastoma (year before diagnosis excluded)

	Cases		Controls		OR*	95% CI†
	N°	%	N°	%		
Day care attendance						
No	340	78	269	72	1.00	reference
Yes	97	22	103	28	0.81	0.56-1.17
Age at starting day care						
No day care	340	78	269	72	1.00	reference
< 6 months	55	13	52	14	0.90	0.57-1.41
≥ 6 months	36	8	42	12	0.72	0.43-1.22
Day care duration						
No day care	340	78	269	72	1.00	reference
< 6 months	9	2	7	2	1.01	0.36-2.83
≥ 6 months	88	20	99	26	0.75	0.52-1.10
Total hours day care exposure‡						
No day-care	340	78	269	72	1.00	reference
< 500 hours	15	3	12	3	0.99	0.44-2.22
≥ 500 hours	82	19	94	25	0.74	0.51-1.09

* Unmatched odds ratios (OR) adjusted for child's diagnosis reference age, mother's race, mother's education and household income at birth year.

† CI: confidence interval.

‡ Total hours day care exposure took into account both day-care duration and number of day care hours attended per week.

TABLE 3. Infectious diseases, allergies and risk of neuroblastoma (children older than one year)

	Cases		Controls		OR*	95% CI*
	N°	%	N°	%		
Infectious diseases						
Selected childhood infections†						
Yes *vs* no	57	17	72	24	0.60	0.39-0.93
0	273	83	231	76	1.00	reference
1	55	17	64	21	0.66	0.42-1.02
2+	2	0.6	9	3	0.13	0.02-0.65
Ear infections						
Yes *vs* no	254	80	210	69	1.76	1.20-2.58
0	65	20	95	31	1.00	reference
< 1 per month	190	61	167	55	1.62	1.09-2.41
≥ 1 per month	55	18	39	13	2.13	1.24-3.66
Other infections‡						
Yes *vs* no	39	12	29	9	1.26	0.74-2.11
Allergies						
Asthma	18	5	25	8	0.69	0.36-1.34
Hay fever	8	2	17	6	0.43	0.18-1.04
Eczema	19	6	21	7	0.82	0.41-1.62
Any allergy§	45	14	58	19	0.68	0.44-1.07

* Unmatched odds ratios (OR) adjusted for child's diagnosis reference age, mother's race, mother's education and household income at birth year, CI: confidence interval.

† Selected childhood infections included chickenpox, mumps, German measles and red measles.

‡ Other infection included upper and lower respiratory tract, digestive and kidney infection (ear infection excluded).

§ Any allergy included asthma, hay fever, other ear throat nose allergiy as rhinitis and sinusitis, eczema, and other dermatological allergy as urticaria, contact dermatitis, food dermatitis and hypersensitivity to drugs.

TABLE 4. Day care attendance, Breastfeeding, Infectious diseases and risk of neuroblastoma

	OR*	95% CI†
Day care attendance (DC) and Breastfeeding (BF)‡		
No DC, no BF	1.0	reference
DC, no BF	0.73	0.44-1.20
No DC, BF	0.63	0.41-0.96
DC, BF	0.46	0.28-0.74
No DC, BF ≤ 6 months	1.0	reference
DC, BF ≤ 6 months	0.82	0.46-1.47
No DC, BF > 6 months	0.90	0.52-1.55
DC, BF > 6 months	0.43	0.20-0.92
Day care duration (DCD) and Breastfeeding (BF)‡		
No DC, BF ≤ 6 months	1.0	reference
DCD < 6 months, BF ≤ 6 months	1.68	0.61-4.63
DCD ≥ 6 months, BF ≤ 6 months	0.65	0.35-1.21
No DC, BF > 6 months	0.89	0.52-1.53
DCD < 6 months, BF > 6 months	0.99	0.19-5.33
DCD ≥ 6 months, BF > 6 months	0.36	0.16-0.81
Infantile disease (ID) and Day care (DC)§		
ID, no DC	0.52	0.28-0.95
ID, DC	0.73	0.37-1.41
Ear infections (EI) and Day care (DC)§		
EI, no DC	1.99	0.69-3.24
EI, DC	1.43	0.46-2.81
Other infections (OI) and Day care (DC)§		
OI, no DC	1.43	1.23-2.94
OI, DC	1.04	0.73-2.34
Infantile disease (ID) and Breastfeeding (BF)§		
ID, no BF	0.37	0.18-0.76
ID, BF	0.93	0.49-1.76
Ear infections (EI) and Breastfeeding (BF)§		
EI, no BF	2.29	1.17-4.50
EI, BF	1.65	0.96-2.86
Other infections (OI) and Breastfeeding (BF)§		
OI, no BF	1.92	0.74-4.96
OI, BF	0.80	0.37-1.74

* Unmatched odds ratios (OR) adjusted for child's diagnosis reference age, mother's race, mother's education and household income at birth year.
† Confidence Interval
‡ DC & BF : Analyses conducted in children older than 6 months
§ Infection & DC / Infection & BF : Analyses conducted in children older than 1 year