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Prenatal and perinatal risk factors for neuroblastoma

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Abstract

Neuroblastoma is a rare embryonal tumor of childhood for which risk factors are not well known. Using a nested case-control design, we investigated prenatal, perinatal, and neonatal risk factors in detail by linking 245 pediatric neuroblastoma cases identified in the Swedish Cancer Register diagnosed 1973-1995 with the Swedish Medical Birth Register. Five living controls per case were randomly selected from the birth registry, matched by gender and age. Increased risks were associated with maternal anemia during pregnancy (odds ratio (OR)=2.95, 95% confidence interval (CI): 1.53, 5.69), neonatal respiratory distress (OR=3.61, 95% CI: 1.41, 9.24), and low (below or equal to 7) 1-minute Apgar score (OR=2.23, 95% CI:1.41, 3.52). Increased risks were limited to cases diagnosed before one year of age. Markers of prenatal, perinatal, and neonatal distress may be associated with neuroblastoma in infancy, but not with diagnoses at 1 year or above.

Keywords

neuroblastoma; prenatal; delayed effects, prenatal exposure; anemia; case-control study

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Novelty/Impact: Using unique personal identification numbers in a Swedish population, we linked 245 cases of neuroblastoma and matched controls with prospectively-collected data about their mothers' pregnancies and childbirth and identified a constellation of conditions related to neonatal distress which were associated with this poorly-understood cancer.

Introduction

Neuroblastoma, a tumor originating from embryonic cells of the neural crest, represents 7.8% of cancers among children less than 15 years old in the United States and is the most common malignancy among children under 1 year of age 1, 2. Tumors usually arise in ganglia of the sympathetic neurons of the peripheral nervous system or in the secretory ganglion cells of the adrenal medulla 1. Before one year in age, cases may display spontaneous regression or benign transformation, even with minimal or no treatment (favorable prognosis), while cases diagnosed after one year tend to have aggressive, high-stage and treatment-refractory disease (unfavorable prognosis) 1. Although some biologic and molecular markers have been correlated with the age at diagnosis and clinical course of tumors 3 4, the etiology of neuroblastoma overall or within prognostic subtypes is poorly understood.

The early onset of neuroblastoma in childhood has prompted studies into the role of prenatal and perinatal factors. About 40% of cases are diagnosed prior to age 1, and over 80% before age 4 1. Familial cases are extremely rare 5, and no consistent environmental risk factors have been demonstrated. Some studies have reported associations with gestational exposure to maternal medications 6 7 8 9, parental occupational exposures 10 11, maternal reproductive history and pregnancy course 12 13 14, delivery method and anesthesia 12 14, low 8 15 or high birthweight 13, and congenital abnormalities 16 17 18-20 13 14, but the findings have been inconsistent. Of interest are reports that prenatal vitamins 21-23 and breastfeeding 24 may lower the risk of neuroblastoma. To further investigate prenatal and perinatal risk factors for neuroblastoma, we utilized prospectively collected records about pregnancy and events surrounding childbirth in the Swedish Medical Birth Register linked to cancer cases reported in the Swedish National Cancer Register and Death Register.

Materials and Methods

Study Population

This nested case-control analysis used linked registers as in previous studies investigating risk factors for leukemia, lymphoma and brain tumors in Swedish children 25-28. The source population included all births in Swedish hospitals during 1973-1995 reported to the Medical Birth Register 29, 30. Personalized identification numbers were used to link the Medical Birth Register31 to the National Cancer Register32, which includes 97% of cancers in Sweden and provides confirmatory pathology reports 33, and to the Swedish Register of Causes of Death34. Eligible cases were all children in the Medical Birth Register who were subsequently diagnosed with neuroblastoma through the year 1995, as ascertained by the Swedish Cancer Register or Death Register. We excluded patients diagnosed by autopsy who did not have a previous clinical diagnosis. Data were not available to identify *in situ* cases. The Birth Register served as the source population for controls and included approximately 1.7 million live births between 1973 and 1995. Five controls were randomly selected for each case, matched by gender and by birth year and month. To be eligible, controls must have survived without a diagnosis of neuroblastoma until the date of diagnosis for the matched case.

Data Collection

By linking neuroblastoma cases and matched controls to the Swedish Medical Birth Register, we gained access to routinely collected information from antenatal, obstetrical, and neonatal medical visits, including maternal demographics and reproductive history, pregnancy course, labor and delivery, and postnatal events. Records begin at the first antenatal visit and end with the newborn's discharge from the hospital.

Data abstracted from birth records included: maternal year of birth, parity, length of gestation, weight gain during pregnancy, and maternal conditions during pregnancy and delivery, coded by checkboxes or according to the Swedish version of the International Classification of Disease, eighth (ICD-8, 1973-1986) or ninth (ICD-9, after 1986) revisions. All ICD-9 codes were recoded to ICD-8 values for analytic purposes. Maternal conditions examined were diabetes (checkbox), epilepsy (checkbox), diseases of the blood (ICD-8 280-289, 632.40, 633), anemia (ICD-8 280-285, 633, 676), hypertension (checkbox), renal disease (checkbox), urinary and other infections (checkbox), preterm labor (ICD-8 634.97) , placental bleeding (ICD-8 632, 651, 770), delivery complications (ICD-8 651-662), postpartum complications (ICD-8 670-678), a diverse group of maternal infections and exposures during pregnancy (ICD-8 761), and other complications of pregnancy (ICD-8 634). Gestational age at birth was calculated as the number of completed weeks, with more than 97% of pregnancy durations determined by the agreement of calculated pregnancy duration and duration stated on the pediatric record 31. Preterm birth was defined as < 37 completed weeks 35. Obstetrical records indicated delivery method and anesthetic use (nitrous oxide or other sedatives, epidural or spinal anesthesia, infiltrative local vaginal anesthesia, paracervical blockade, pudendal blockade, or petidin), infant gender, birth length and weight, neonatal head circumference, Apgar scores 36 at 1 and 5 minutes after birth*, congenital abnormalities (ICD-8 740-759), neonatal respiratory distress (ICD-8 776), interventions including neonatal ventilation and supplemental oxygen (checkbox), hemolytic disease with (ICD-8 774) or without (ICD-8 775) kernicterus, and jaundice (checkbox). No information was available on prenatal alcohol use, while smoking was only reported from 1982 onward. Clinical reporting of all cases of cancer is mandatory at public and private hospitals and treating institutions in Sweden. Additionally, pathologists and cytologists also report each malignant diagnosis on biopsies or other specimens to the Cancer Registry 32. The Cancer Registry collects the name, personal identification number, sex, hospital site, date of diagnosis, site of tumor, histologic type (by ICD-7 code (WHO/HS/CANC/24.1 Histology Code before 1993, and ICD-O-2 thereafter 32)), primary site (by ICD-7 codes 32), basis of diagnosis, whether cancer proved fatal, and whether autopsy proved the sole basis for diagnosis. Tumor stage at diagnosis was not collected during the study years.

Statistical analysis

Conditional logistic regression was used to calculate odds ratios (OR) and 95 percent confidence intervals (CI) as an estimate of relative risk (RR) using Epicure (Hirosoft,

*The Apgar score comprises color (appearance), heart rate (pulse), responsiveness to stimuli (grimace), muscle tone (activity), and respiratory effort. 36. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32(4): 260-7.

Seattle, WA). Risks for neuroblastoma were evaluated for all cases combined and stratified by age at diagnosis (<365 days or ≥ 365 days; ≤1 month or 1 month to 1 year) and by primary site of disease: adrenal gland (ICD 195.0), peripheral nerves of the sympathetic nervous system (ICD 193.3), or brain (ICD 193.0). Nine children with tumors identified on autopsy (where there was no previous suspicion of a tumor) were excluded from analysis. Tumors of unspecified, uncoded, other, or multiple sites were grouped. Analyses were univariate with matching on gender, birth year and birth month, except where multivariate analyses are noted. Multivariate analyses were performed with maternal anemia, 1-minute Apgar score (<7 vs 7+), neonatal respiratory distress, and supplemental oxygen. Results presented in tables are for exposures with at least 3 exposed cases and 3 exposed controls from matched univariate analyses.

Results

There were 245 cases of neuroblastoma diagnosed during 1973-1995 in the Swedish Cancer Register: 62 arising in the adrenal gland, 118 in peripheral nerves of the sympathetic nervous system, 33 in the brain or cranial nerves, and 32 in other sites (Table 1). The mean age at diagnosis was 2 years 9 months, and 53% of cases were male. Male-to-female ratio was highest in the adrenal site. Tumors arising in the brain were diagnosed at an older mean age and had the highest 3-year survival rate. Eighty-two percent of all cases survived beyond 3 years from diagnosis.

Neuroblastoma cases did not differ from controls with respect to maternal age or parity, gestational age (Table 2), or maternal weight gain during pregnancy (data not shown). Maternal anemia in pregnancy was associated with an increased risk of neuroblastoma (OR=2.72, 95% CI:1.36-5.44, 15 cases), more so for cases diagnosed before age 1 (OR=3.89, 95% CI: 1.40-10.9, 7 cases) than after 1 (Table 2). Maternal hypertension of pregnancy (pre-eclampsia, eclampsia, or toxemia) was associated with a significantly decreased risk of neuroblastoma overall (OR=0.36, 95% CI: 0.15-0.87, 6 cases), while nonsignificant decreases were seen in cases diagnosed before or after age 1. Maternal conditions not associated with neuroblastoma included bleeding disorders, imminent preterm labor, placental bleeding, and a diverse group of maternal exposures during pregnancy (ICD 761).

Method of delivery (spontaneous vaginal, instrumental vaginal, or Caesarian section) was not associated with neuroblastoma, nor was use of anesthetic agents, including nitrous oxygen, petidin, narcotics, or epidural, pudendal blockade, or infiltrated local anesthesia during delivery (Table 3). Paracervical blockade was associated with increased risk for neuroblastoma diagnosed before 1 year (OR=3.45, 95% CI: 1.57-7.57, 14 cases), but was not associated with risk in the overall group.

Low (<2500 or <2000 grams) or high (≥4000 or ≥4500 grams) birth weights were not associated with neuroblastoma on univariate analyses or in the multivariate predictive model incorporating gestational age, maternal nationality, and parity (Table 4). Birth length and head circumference were not associated with neuroblastoma overall; however, large (>37

cm) head circumference was associated with increased risk of adrenal tumors (OR=2.87, 95% CI: 1.30-6.30, 7 cases) (Table 5).

Apgar score ≤ 7 at 1 minute after birth was associated with neuroblastoma (OR=1.82, 95% CI: 1.12-2.98, 24 cases), primarily for tumors arising before 1 year (OR=3.07, 95% CI 1.53-6.18, 14 cases) but not ≥ 1 year (Table 4). Five minutes after birth, low (≤ 7) Apgar scores did not convey an increased risk.

Neonatal respiratory distress, including aspiration, hyaline membrane disease, intrauterine anoxia, or other causes (ICD 776), was marginally associated with neuroblastoma (OR=2.66, 95% CI: 0.96-7.41, 6 cases), with a stronger effect in cases diagnosed before age one (OR=4.20, 95% CI: 1.19-14.8, 5 cases). Supplemental oxygen therapy was not significantly associated with neuroblastoma. Neonatal hemolytic disease was associated with a nonsignificantly increased risk of neuroblastoma overall (OR=1.66, 95% CI: 0.92-2.98, 16 cases), an effect limited to cases in which kernicterus developed (OR= 3.13, 95% CI: 1.02-9.57, 5 cases). In multivariate analyses incorporating low (≤ 7) 1-minute Apgar scores, neonatal respiratory distress, and maternal anemia, the risks associated with low 1-minute Apgar scores and maternal anemia remained significantly increased for tumors arising before one year of age. There was no independent effect of supplemental oxygen therapy or neonatal respiratory distress when added to this multivariate model. Adjusting 1- or 5-minute Apgar scores for method of delivery to account for different Apgar scores after Caesarian section did not meaningfully change any associations.

Congenital abnormalities overall were not associated with neuroblastoma, nor were cardiovascular (2 cases) or limb defects (4 cases). Neonatal factors not associated with neuroblastoma included jaundice, preterm delivery (<37 completed weeks), and postmaturity (≥43 completed weeks). There were insufficient numbers (fewer than 4 cases) to evaluate associations with a number of maternal or infant conditions: urinary or respiratory diseases and infections, nervous system disorders, prior maternal abortions, premature labor or induction of labor, use of incubators or other resuscitation, scalp vein infusion, or blood transfusion. No meaningful differences in effect were seen by gender. Associations of prenatal and perinatal factors with neuroblastoma diagnoses in specific sites are presented in Table 5.

For cases diagnosed in the first month of life, the association with low 1-minute Apgar score was significant (OR=6.67, 95% CI: 1.90, 23.4, 7 cases), while the association was only suggestive for cases diagnosed during months 2 to 12 (OR=2.28, 95% CI: 0.91, 5.69, 7 cases). The marginal risk associated with neonatal respiratory distress was limited to cases diagnosed during months 2 to 12 (OR=4.02, 95% CI: 0.98, 16.5, 4 cases). Analyses stratified by duration of survival did not improve the prediction of case status, although low 1-minute Apgar score and childhood birth defects were associated with short survival <3 years. Maternal anemia and Caesarian section were associated with longer survival. Crossing age at diagnosis (<1 year or ≥ 1 year) and survival (< 3 years or ≥ 3 years) did not yield any stratum that predicted case status better than age at diagnosis alone. There were no meaningful changes in associations over the different treatment eras (1973-80, 1980-89, 1990-95) .

Discussion

This population-based record-linkage study in Sweden found that cases of neuroblastoma diagnosed before 1 year of age were associated with a constellation of prenatal and perinatal factors including maternal anemia, hemolysis, low 1-minute Apgar scores and neonatal respiratory distress. No prenatal or perinatal risk factors were identified for cases diagnosed above one year of age.

Our findings are consistent with some prior studies of neuroblastoma. In one large case-control study, an association was seen with maternal anemia during pregnancy, 12, although another study reported a null association 21. Our finding is noteworthy since anemia of pregnancy is largely due to nutritional iron or folate deficiency 37, 38, while prenatal multivitamin use has been associated with a decreased risk of neuroblastoma 21, 22 and with primitive neuroectodermal brain tumors (including neuroblastoma) 39. In addition, folate fortification of grain has been correlated with a decrease in neuroblastoma incidence in Canada, based on an interventional time series analysis 40. While our study did not address prenatal supplement use, it is likely that maternal anemia reflects a lack of nutritional iron and/or folate during a time of increased metabolic demand.

The excess risk we observed for low Apgar score is, to our knowledge, a new finding for neuroblastoma, and part of a spectrum of conditions related to neonatal distress. One prior study reported a non-significantly increased risk of neuroblastoma with very low (≤3) 1-minute Apgar score, but not for scores of 4-6 41. In an effort to distinguish symptoms of neonatal distress from symptom-directed interventions, as previously recommended 25, we assessed the contribution of supplemental oxygen therapy in multivariate analyses incorporating neonatal respiratory distress. However, oxygen was not independently associated with neuroblastoma and did not measurably change the effect of respiratory distress. Due to the concern that neonatal distress may develop secondary to an existing tumor mass, we analyzed tumors diagnosed within the first month of life *vs.* those diagnosed between 1 month and 1 year. Our aim was to see whether distress symptoms at birth clearly tracked with cancer diagnosis during the first month of life. The statistically significant association of low Apgar score with neuroblastoma diagnoses before 1 month may be due to pulmonary effects from an unrecognized abdominal mass, but both low 1-minute Apgar score and respiratory distress shared borderline significant associations with diagnoses during months 2-12 as well.

Maternal anemia along with neonatal respiratory distress may decrease blood oxygen-carrying capacity during gestation and the perinatal period, thus interfering with the maturation of neural crest-derived tissues. The intracellular response to hypoxia via stabilization of the hypoxia-inducible factors (HIF-1α and HIF-2α) suggests that genes expressed in response to oxygen deprivation may play a role in solid tumor induction 42 43. Subunits of HIF have been shown to accumulate in response to hypoxic conditions in human neuroblastoma cell lines 44, 45 with associated dedifferentiation 44. Our finding of an elevated risk of neuroblastoma associated with neonatal hemolytic states, as previously described in case series 20, would be consistent with this mechanism.

We replicated previous null associations reported between maternal age and neuroblastoma 8, 17, 21, 41 14. However, we did not confirm associations reported with placental bleeding in the third trimester, epidural anesthesia, threatened miscarriage, Caesarian delivery 12, 13, 41, gestational diabetes 14, hypertension in pregnancy 7, 46, or firstborn status 13. Nor did we replicate previous associations of neuroblastoma with congenital anomalies 14, 16, 18, 19, 47-50 except for a limited finding among patients with <3 years' survival after diagnosis. Concerns have been raised that some clinically insignificant tumors may be diagnosed incidentally during the evaluation of a congenital abnormality or other condition 14, such as during neuroblastoma screening programs for some countries like Japan 51, or during post-mortem examinations. By eliminating autopsy-only diagnoses, we helped to eliminate this possible bias.

Our study benefited from the incorporation of prospectively recorded medical and demographic data routinely collected during obstetrical visits. This approach avoids differential recall of perinatal events between cases and controls, or between cases with a recent *vs.* remote diagnosis. The large population-based pool of births and nested study design permitted selection of matched controls from the same source population as cases.

Limitations of this study included the small number of pregnancies with exposure to infections or medications, or with history of prior abortion. Due to the small number of cases and multiple comparisons, some associations may have resulted from chance events, especially in relation to site-specific diagnoses, e.g. adrenal gland or peripheral sympathetic nerves. The high proportion of cases with neuroblastoma of the brain (52%) diagnosed during 1990-1995, when neuroimaging was more widespread than in earlier study years 52 raises the possibility of ascertainment bias. Other limitations of the study included the difficulty of determining the specific timing of events during pregnancy 53, and the lack of tumor staging classification in the Swedish cancer registry.

In summary, this population-based linked-registry study of neuroblastoma in Sweden identified maternal anemia, neonatal hemolytic disease, low 1-minute Apgar score, and neonatal respiratory distress as risk factors for cases diagnosed under 1 year of age. These perinatal conditions were not associated with the typically more aggressive and treatment-resistant cases of neuroblastoma diagnosed after 1 year of age, which should be the focus of further larger studies.

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Abbreviations used

OR	odds ratio
CI	confidence interval
ICD	International Classification of Disease
RR	relative risk
cm	centimeter
HIF	hypoxia-inducible factor

Table 1

Distribution of neuroblastoma cases according to site of tumor by age at diagnosis, gender, year of diagnosis, and survival.

Characteristic	All cases (n=245)		Adrenal (n=62)		Peripheral nerves (n=118)		Brain (n=33)		Other sites (n=32)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Age at diagnosis										
< 1 month	31	13%	15	24%	13	11%	0	0	3	9%
1 month - 1 year	75	31%	17	27%	44	37%	6	18%	8	25%
>1 year	139	57%	30	48%	61	57%	27	82%	21	66%
Mean (months)	*32.9 ± 48.5*		*18.0 ± 21.9*		*23.4 ± 31.0*		*92.4 ± 82*		*36.0 ± 49.5*	
Gender										
Male	131	53%	37	60%	61	52%	17	52%	16	50%
Female	114	47%	25	40%	57	48%	16	48%	16	50%
Birth year										
1973-1979	85	35%	17	27%	48	41%	14	42%	6	19%
1980-1989	92	38%	22	35%	43	36%	15	45%	12	38%
1990-1995	68	28%	23	37%	27	23%	4	12%	14	44%
Year of diagnosis										
1973-1979	54	22%	14	23%	33	28%	4	12%	3	9%
1980-1989	89	36%	21	34%	46	39%	12	36%	10	31%
1990-1995	102	42%	27	44%	39	33%	17	52%	19	59%
Survival after diagnosis										
<3 years	43	18%	18	29%	20	17%	1	3%	4	13%
3+ years	202	82%	44	71%	98	83%	32	97%	28	88%
Prognosis [1]										
Favorable	82	33%	23	37%	45	38%	5	15%	9	28%
Intermediate	144	59%	30	48%	65	55%	28	85%	21	66%
Unfavorable	19	8%	9	15%	8	7%	0	0	2	6%

[1] Prognosis variable was created based on age at diagnosis and survival, as described in Methods section.

TABLE 2

Risk of neuroblastoma associated with maternal conditions and pregnancy characteristics by age at diagnosis.

	All neuroblastoma (n=245)			Diagnosis before 1 year (n=106)			Diagnosis at 1 year or older (n=139)		
	Controls No.	Cases No.	OR (95% CI)[1]	Controls No.	Cases No.	OR (95% CI)	Controls No.	Cases No.	OR (95% CI)
Maternal age (years completed)									
<20	59	7	0.58 (0.26, 1.29)	24	1		35	6	0.86 (0.35, 2.12)
20 - 34	1053	214	1.00	457	95	1.00	596	119	1.00
35+	113	24	1.04 (0.65, 1.65)	49	10	0.98 (0.48, 2.00)	64	14	1.09 (0.59, 2.01)
Maternal parity									
1	534	104	1.00	227	41	1.00	307	63	1.00
2-3	611	118	0.99 (0.75, 1.32)	273	54	1.09 (0.70, 1.68)	338	64	0.92 (0.63, 1.35)
≥ 4	80	23	1.48 (0.89, 2.45)	30	11	2.04 (0.94, 4.41)	50	12	1.17 (0.59, 2.31)
Gestational age (completed weeks)									
< 37	61	11	0.90 (0.47, 1.74)	31	3	0.47 (0.14, 1.56)	30	8	1.39 (0.61, 3.16)
37- 42	1121	223	1.00	484	100	1.00	641	123	1.00
≥ 43	36	11	1.53 (0.77, 3.02)	13	3	1.12 (0.31, 4.02)	24	9	1.93 (0.88, 4.22)
Maternal anemia during pregnancy									
No	1200	232	1.00	520	99	1.00	680	133	1.00
Yes	25	13	2.72 (1.36, 5.44)	10	7	3.89 (1.40, 10.9)	15	6	2.04 (0.78, 5.34)
Maternal hypertension									
No	1150	239	1.00	495	103	1.00	655	136	1.00
Yes	75	6	0.36 (0.15, 0.87)	35	3	0.37 (0.10, 1.32)	40	3	0.36 (0.11, 1.18)

[1]OR, odds ratio; CI, confidence interval.

TABLE 3

Risk of neuroblastoma associated with method of obstetrical delivery and anesthesia by age at diagnosis.

	All neuroblastoma (n=245)			Diagnosis before 1 year (n=106)			Diagnosis at 1 year or older (n=139)		
	Controls No.	Cases No.	OR (95% CI)[1]	Controls No.	Cases No.	OR (95% CI)	Controls No.	Cases No.	OR (95% CI)
Method of delivery									
Spontaneous vaginal	1019	201	1.00	439	87	1.00	580	114	1.00
Instrumental vaginal	66	18	1.39 (0.80, 2.38)	24	8	1.69 (0.73, 3.89)	42	10	1.23 (0.60, 2.52)
Caesarian section	43	9	1.07 (0.50, 2.26)	28	4	0.71 (0.24, 2.10)	15	5	1.75 (0.60, 5.08)
Unknown	97	17		39	7		58	10	
Epidural anesthetic									
No	1100	215	1.00	469	92	1.00	631	123	1.00
Yes	125	30	1.25 (0.80, 1.94)	61	14	1.19 (0.62, 2.27)	64	16	1.30 (0.71, 2.37)
Narcotics during delivery									
No	1201	237	1.00	520	103	1.00	681	134	1.00
Yes	24	8	1.77 (0.75, 4.17)	10	3	1.57 (0.40, 6.26)	14	5	1.91 (0.64, 5.71)
Paracervical blockade									
No	1147	225	1.00	501	92	1.00	646	133	1.00
Yes	78	20	1.42 (0.79, 2.58)	29	14	3.45 (1.57, 7.57)	49	6	0.51 (0.19, 1.35)

[1] OR, odds ratio; CI, confidence interval.

TABLE 4

Risk of neuroblastoma associated with birth measurements, Apgar score, and other neonatal conditions by age at diagnosis.

	All neuroblastoma (n=245)			Diagnosis before 1 year (n=106)			Diagnosis at 1 year or older (n=139)		
	Controls No.	Cases No.	OR (95% CI)[1]	Controls No.	Cases No.	OR (95% CI)	Controls No.	Cases No.	OR (95% CI)
Birth weight (grams)									
< 2500	43	9	1.05 (0.51, 2.19)	19	5	1.33 (0.49, 3.64)	24	4	0.83 (0.28, 2.45)
2500 - <4500	1132	225	1.00	489	96	1.00	643	129	1.00
≥ 4500	47	10	1.07 (0.53, 2.18)	21	4	0.97 (0.32, 2.89)	26	6	1.15 (0.46, 2.91)
unknown	3	1		1	1		2	0	
1-minute Apgar score									
>7	1148	217	1.00	500	89	1.00	648	128	1.00
≤ 7	70	24	1.82 (1.12, 2.98)	26	14	3.07 (1.53, 6.18)	44	10	1.15 (0.56, 2.36)
Unknown	7	4		4	3		3	1	
5-minute Apgar score									
>7	1197	235	1.00	516	99	1.00	681	136	1.00
≤ 7	15	4	1.39 (0.45, 4.26)	7	2	1.62 (0.33, 7.92)	8	2	1.26 (0.26, 6.17)
Unknown	13	6		7	5		6	1	
Respiratory distress									
No	1213	239	1.00	523	101	1.00	695	139	1.00
Yes	12	6	2.66 (0.96, 7.41)	7	5	4.20 (1.19, 14.8)	5	1	
Supplemental oxygen therapy									
No	1208	241	1.00	522	103	1.00	686	138	1.00
Yes	17	6	1.18 (0.40, 3.50)	8	3	1.88 (0.50, 7.09)	9	1	
Jaundice									
No	1125	227	1.00	490	99	1.00	635	128	1.00
Yes	100	18	0.89 (0.53, 1.51)	40	7	0.86 (0.37, 2.00)	60	11	0.91 (0.46, 1.79)

	All neuroblastoma (n=245)			Diagnosis before 1 year (n=106)			Diagnosis at 1 year or older (n=139)		
	Controls No.	Cases No.	OR (95% CI)[1]	Controls No.	Cases No.	OR (95% CI)	Controls No.	Cases No.	OR (95% CI)
Hemolytic disease with kernicterus									
No	1217	240	1.00	526	104	1.00	691	136	1.00
Yes	8	5	3.13 (1.02, 9.57)	4	2	2.51 (0.46, 13.7)	4	3	3.77 (0.84, 16.8)
Hemolytic disease without kernicterus									
No	1183	234	1.00	515	103	1.00	668	131	1
Yes	42	11	1.34 (0.67, 2.69)	15	3	1.00 (0.28, 3.56)	27	8	1.55 (0.67, 3.59)
Any birth defect									
No	1168	232	1.00	505	98	1.00	663	134	1.00
Yes	57	13	1.15 (0.62, 2.15)	25	8	1.67 (0.72, 3.86)	32	5	0.77 (0.29, 2.03)
Cardiac defects									
No	1217	243	1.00	525	105	1.00	692	138	1.00
Yes	8	2	1.26 (0.26, 6.17)	5	1		3	1	
Limb anomalies									
No	1200	241	1.00	516	102	1.00	684	139	
Yes	25	4	0.80 (0.28, 2.30)	14	4	1.43 (0.47, 4.34)	11	0	

[1] OR, odds ratio; CI, confidence interval.

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Table 5

Risk of neuroblastoma by site of diagnosis associated with selected conditions of pregnancy and the perinatal period.

	Adrenal gland (n=62)			Peripheral nerves (n=118)			Brain (n=33)		
	Controls No.	Cases No.	OR (95% CI)	Controls No.	Cases No.	OR (95% CI)	Controls No.	Cases No.	OR (95% CI)
Maternal anemia during pregnancy									
No	302	57	1.0	581	113	1.0	160	33	
Yes	8	5	2.19 (0.88, 5.46)	9	5	1.86 (0.76, 4.54)	5	0	
Birth weight (grams)									
< 2500	11	2	0.90 (0.22, 3.68)	23	3	0.65 (0.21, 2.05)	4	3	2.06 (0.63, 6.76)
2500 - <4500	287	56	1.0	541	109	1.0	154	29	1.0
≥ 4500	11	4	2.00 (0.72, 5.50)	25	5	0.76 (0.31, 1.87)	7	1	
1-minute Apgar score									
>7	289	54	1.0	553	104	1.0	153	31	1.0
≤ 7	18	7	1.91 (0.87, 4.19)	34	12	1.64 (0.90, 2.98)	12	2	0.83 (0.20, 3.46)
Unknown	3	1		3	2	2.56 (0.63, 10.37)	0	0	
Head circumference									
<32 cm	14	1		13	1		4	2	1.58 (0.38, 6.61)
32-37 cm	281	53	1.0	544	107	1.0	155	29	1.0
>37 cm	13	7	2.87 (1.30, 6.30)	27	6	0.99 (0.43, 2.25)	5	2	1.48 (0.35, 6.19)
Hemolytic disease without kernicterus									
No	302	61		563	110	1.0	159	31	1.0
Yes	8	1		27	8	2.01 (0.98, 4.13)	6	2	1.75 (0.42, 7.30)