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Assessment of risk factors for infantile cataracts using a case-control study, National Birth Defects Prevention Study, 2000–2004

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Abstract

Objective—To identify risk factors for infantile cataracts of unknown etiology.

Design—Case-control study

Participants—Case-infants (N=152) and control-infants (N=4205) enrolled in the National Birth Defects Prevention Study for birth years 2000–2004.

Methods—Multivariate analysis was performed exploring associations for risk factors for bilateral and unilateral infantile cataracts of unknown etiology.

Main Outcome Measures—Infantile cataracts of unknown etiology

Results—Maternal interviews were completed for 43 case-infants with bilateral and 109 with unilateral infantile cataracts of unknown etiology. Very low birth weight (<1500g) was associated with both unilateral (adjusted odds ratio [OR]=6.0; 95% confidence interval [CI]=2.2–16.3) and bilateral (OR=13.2; 95% CI=4.2–41.1) cataracts, while low birth weight (1500–2499g) was only associated with bilateral cataracts (OR=3.3; 95% CI=1.3–8.1). Infants with unilateral cataracts were more likely to be born to primigravid women (OR=1.6; 95% CI=1.0–2.7) than women with

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The coding of drug information in the NBDPS used the Slone Drug Dictionary, under license from the Slone Epidemiology Center at Boston University, Boston.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

two or more previous pregnancies, although this was of borderline significance. While not statistically significant, effect estimates were elevated suggesting a possible association between unilateral cataracts and maternal substance abuse during pregnancy, and between bilateral cataracts and urinary tract infection during pregnancy and aspirin use during pregnancy.

Conclusions—Very low birth weight is associated with both bilateral and unilateral cataracts, while low birth weight is associated with bilateral cataracts and primigravidity with unilateral cataracts. Other associations, while not of statistical significance, suggest risk factors that merit further research.

Cataract is the second most common cause of preventable blindness in children worldwide, second only to corneal scarring.¹ The preferred treatment of visually significant infantile cataracts is cataract extraction and in developed countries where earlier detection and treatment are pursued, infantile cataracts are becoming a less common cause of permanent visual impairment.² The birth prevalence of infantile cataracts has been reported to range from 1.2 to 6.0 cases per 10,000 births.² Known risk factors for infantile cataracts include genetic and metabolic disorders, intrauterine infection, and trauma or exposure to certain medications or radiation that occur postnatally.² However, for most cases, the etiology is unknown. Studies have shown that up to half of bilateral cataracts^{3, 4} and over half of unilateral cataracts^{3–6} are of unknown cause. Because infants with cataracts are much more likely to be of low birth weight^{6–8} we examined the association between several risk factors for low birth weight (e.g., infection,^{9, 10} maternal age,¹¹ diabetes,¹² smoking,^{11, 13–15} and maternal alcohol consumption¹⁶) and infantile cataracts.

METHODS AND MATERIALS

For this analysis, we used data from the National Birth Defects Prevention Study (NBDPS), an ongoing multi-site case-control study of genetic and environmental risk factors for major birth defects. Because they are relatively rare events, birth defects are most efficiently studied using a case-control design. Detailed methods of the study have been reported elsewhere.¹⁷ Case-infants are diagnosed with at least one of over 30 eligible birth defects and were identified from population-based birth defects surveillance systems in ten sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah). Case information abstracted from medical records includes demographic data, growth parameters, major and minor birth defects, method(s) of diagnosis, laboratory results, and family history. Because the goal of the NBDPS is to identify risk factors for birth defects, case-infants with recognized or strongly suspected single-gene disorders or chromosome abnormalities are excluded from the study. For inclusion in the NBDPS, infantile cataract(s) must be diagnosed by an ophthalmologist within the first twelve months of life. Identification of cataracts was based on routine, clinical care; no screening of either case-infants or control-infants was specifically conducted for this study. Infants with cataracts secondary to ophthalmic surgery or trauma or with minor lens opacities not requiring further follow-up or intervention were excluded. Infants with cataracts who had a family history consistent with a Mendelian pattern of inheritance were included in the NBDPS during this time period; however, we excluded infants who had a first degree relative with infantile cataracts from these analyses. In addition to a routine case review by clinical geneticists at each study site, a single clinical geneticist (SAR) reviewed clinical data on case-infants with cataracts to ensure each infant met the case definition and to classify infants according to whether cataracts occurred as an isolated defect or as one of multiple, unrelated major birth defects.¹⁸

Control-infants were live born with no major birth defects. Control-infants were randomly selected from either birth certificates or birth hospital records from the same source population and time period as the case-infants, and a recent analysis has shown that they are

representative of the source population.¹⁹ Mothers of case- and control-infants were asked to participate in a detailed telephone interview that included questions on demographic factors, family history of birth defects, nutrition, lifestyle factors, illnesses, and medication use. Interviews were conducted between 6 weeks and 24 months after the estimated date of delivery (EDD).

SAS v9.1 (SAS Institute Inc., Cary, NC) was used to perform all analyses. We included case- and control-infants enrolled in NBDPS with birth dates on or after January 1, 2000 and with an EDD on or before December 31, 2004. Case-infants were divided into two categories (unilateral and bilateral cataracts) and risk factor analyses were performed for each of these categories. We looked at risk factors reported as present any time during the pregnancy and because it is unclear if a certain period of lens development is more susceptible to the formation of cataracts, we further categorized the risk factors by timing into first, second and third trimesters. Because certain infections (e.g., rubella) substantially increase the risk for infantile cataracts and information needed to look at specific infections (such as results of specific antibody titers of the mother and child) were often not available, we used maternal report of infection and other surrogates (e.g., maternal report of fever or use of certain medications). Mothers were classified as having an infection during pregnancy if they reported the presence of any type of infection during this time period (maternal infection during pregnancy [yes, no]). In addition, we divided maternal infection into respiratory (maternal respiratory illness during pregnancy [yes, no]) and non-respiratory infections.²⁰ Because all non-respiratory infections among mothers of case-infants were noted to be urinary tract infections (UTI), we explored maternal UTI during pregnancy (yes, no). We also looked at reported maternal fever during pregnancy (yes, no) and reported use of anti-infectives (including antibiotics, antivirals, and antiparasitics) (yes, no), antitussives (including both expectorants and mucolytics) (yes, no) and antipyretics (i.e., acetaminophen, aspirin and ibuprofen) (yes, no) during pregnancy. We were unable to explore the association between pre-pregnancy diabetes and infantile cataracts because none of the mothers of case-infants had pre-pregnancy diabetes, thus we only looked at gestational diabetes (yes, no) in our risk factor analysis. We also explored other risk factors including infant birth weight (very low birth weight [<1500 g], low birth weight [1500 – 2499 g], normal birth weight [2500 – 3999 g] and macrosomia [>3999 g]), sex (male, female), maternal age at delivery (<25 , 25 – 34 , and >34 years), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), body mass index (BMI) (underweight [<18.5], normal [$18.5 \leq \text{BMI} < 25$], overweight [$25 \leq \text{BMI} < 30$], obese [≥ 30]), maternal education (less than or greater than a high school education), gravidity (1, 2, >2), reported maternal tobacco, alcohol or illicit drug use during pregnancy (yes, no) and study center. Univariate analysis was used to assess each risk factor. We created our final model using multivariate logistic regression. We adjusted for potential confounding by removing each variable from the model one at a time. If removing the variable resulted in a change in the effect estimate (OR) of more than 10%, it was placed back in the model.

Each participating site received institutional review board(s) approval for this study.

RESULTS

For birth years 2000–2004, there were 187 eligible case-infants with infantile cataracts and 4209 control-infants in the NBDPS. Thirty-five case-infants (1 with unilateral and 34 with bilateral cataracts) and four control-infants reportedly had a first-degree relative with infantile cataracts and were excluded from these analyses (Table 1). Of those case-infants without a first-degree relative with infantile cataracts, 72% ($N=109$) had unilateral and 28% ($N=43$) had bilateral involvement. Of those case-infants with unilateral cataracts, 95% ($N=104$) had cataracts as an isolated birth defect and 5% ($N=5$) had cataracts as one of

multiple congenital anomalies. Of those case-infants with bilateral cataracts, 77% (N=33) had cataracts as an isolated birth defect and 23% (N=10) had cataracts as one of multiple birth defects. Isolated cataracts were more commonly unilateral than bilateral and cataracts associated with multiple major birth defects tended to be bilateral compared to unilateral ($p=0.001$).

After the exclusions detailed above, the risk factor analyses included 152 case-infants with infantile cataracts and 4205 control-infants. When we looked at the crude associations between various potential risk factors categorized into first, second and third trimester exposures and infantile cataracts, the numbers were very small and not of statistical significance; thus we performed multivariate logistic regression analyses looking at exposure at any time during pregnancy as the exposure of interest for each potential risk factor. In our final models for both unilateral and bilateral infantile cataracts, each risk factor was adjusted for all of the other risk factors in their respective models (Table 2 and 3).

Unilateral cataracts were most strongly associated with very low birth weight (adjusted odds ratio [OR]=6.0; 95% confidence interval [CI]=2.2–16.3) (Table 2). Infants with unilateral cataracts were more likely to be born to primigravid women (OR=1.6; 95% CI=1.0–2.7) than women with two or more previous pregnancies, although this finding was of borderline statistical significance. Report of a respiratory illness during pregnancy was inversely associated with unilateral cataracts (OR=0.6; 95% CI=0.4–1.0), although this finding was not statistically significant. Among the other risk factors examined, substance abuse during pregnancy had an elevated effect estimate (OR=2.1; 95% CI=0.9–4.8), but it did not show a statistically significant association with unilateral cataracts.

Bilateral cataracts were associated with both very low birth weight (OR=13.2; 95% CI=4.2–41.1) and low birth weight (OR=3.3; 95% CI=1.3–8.1) (Table 3). Women who reported a UTI during pregnancy (OR=1.7; 95% CI=0.8–3.7) and women who reported aspirin use during pregnancy (OR=2.0; 95% CI=0.6–6.8) were more likely to have an infant with bilateral cataracts, though these findings were not statistically significant.

DISCUSSION

In our analysis, both very low birth weight (<1500 g) and low birth weight (1500–2499 g) were associated with bilateral cataracts, while only very low birth weight was associated with unilateral cataracts. For unilateral cataracts, effect estimates were slightly elevated for primigravidity and maternal substance abuse, but these findings were of borderline statistical significance. For bilateral cataracts, effect estimates suggested a two-fold association for any reported aspirin use during pregnancy, although this finding was not statistically significant.

Other studies have also noted that rates of bilateral infantile cataracts were higher in those infants with a birth weight <1500g,⁸ <2000g,⁷ or ≤ 2500 g,⁶ although none found an association between low birth weight and unilateral cataracts. This may be due to the higher cut-off values used for low birth weight in these studies; in the two studies that reported their findings for unilateral cataracts, infants of low birth weight as defined by each of these studies (<2000g⁷ and ≤ 2500 g)⁶ appeared to have an increased risk for unilateral cataracts, although these findings did not reach statistical significance (risk ratio =1.60; 95% CI=0.81–3.16)⁷ and ($p=0.08$).⁶ It is possible that the association we observed between low birth weight and infantile cataracts is related to routine screening for retinopathy of prematurity among preterm infants.²¹ Premature infants may be more likely to be diagnosed with cataracts, especially those that may be more mild in nature, and be diagnosed earlier in life than those that do not require routine screening for retinopathy of prematurity.

Even though the risk of unilateral cataracts was slightly elevated for primigravidity, this finding was of borderline statistical significance. Similar to our findings, another study of risk factors for infantile cataracts also noted that the mean birth order was lower in cases with an isolated congenital cataract compared with both population and malformed controls.²²

Other risk factors examined included gestational diabetes, maternal smoking and alcohol use. We saw no evidence of an association between maternal gestational diabetes and infantile cataracts in our study, in contrast to an animal model that showed that 90–95% of rat fetuses born to dams with gestational diabetes had congenital cataracts.²³ Our study, similar to a study in Denmark, did not find an association between infantile cataracts and maternal smoking.⁷ We found that women who had infants with unilateral cataracts were more likely to report using alcohol and illicit substances during pregnancy, although these findings were not statistically significant. It is possible that these associations might be more pronounced in those who also smoked during pregnancy, as one study has suggested that low birth weight may be more strongly associated with alcohol consumption among women who smoke.²⁴ We were unable to further explore these potential interactions within the sample size of our study; however, future studies looking at the interaction between alcohol, substance abuse and smoking are merited.

Even though certain infections during pregnancy have been shown to be associated with low birth weight, and specific infections (e.g., rubella) are known to be risk factors for infantile cataracts,^{25–28} we did not find any statistically significant associations between surrogates of maternal infection (e.g., maternal reports of infection, fever, or use of certain medications during pregnancy) and infantile cataracts. One study found that influenza, the common cold, and respiratory illness during pregnancy were associated with isolated congenital cataracts.²⁹ Because these findings were not found in those who received anti-fever medications, the authors hypothesized that fever might be the common denominator leading to these cases of isolated cataracts. Another study looked at birth order and seasonal variation as proxies for exposures to infections during pregnancy and found no clear association.⁷ We found that those infants of mothers who reported at least one UTI during pregnancy were more likely to have bilateral cataracts, while those who reported a respiratory illness during pregnancy were less likely to have unilateral cataracts, but these findings did not reach statistical significance. Thus, to better understand the contribution that maternal infections make to the etiology of infantile cataracts, it is likely that more specific indicators (e.g., analysis of infant specimens for biological markers of infection) will be needed. Through this analysis, we noted that, while not statistically significant, mothers of infants with bilateral cataracts were more likely to have used aspirin during pregnancy. Among the three cases of bilateral cataracts with reported maternal use of aspirin, indications for their use were not noted. Aspirin is prescribed for some pregnant women with antiphospholipid syndrome,³⁰ pregnancy induced hypertension,^{31, 32} and recurrent intrauterine growth retardation,³³ among other indications. It would be worthwhile to look at the underlying conditions for which those women used aspirin and to evaluate their association with infantile cataracts.

Differences between factors associated with unilateral and bilateral infantile cataracts may help elucidate their etiologies. In our study, nearly all case-infants identified by the NBDPS with a family history of infantile cataracts had bilateral involvement. Other studies have also shown that most infants with cataracts associated with genetic conditions have bilateral cataracts.^{4, 5} We observed that isolated cataracts tended to be unilateral and cataracts associated with multiple major birth defects were more likely bilateral, a finding similar to that of a previous study in the United States.⁸ This suggests a different etiology for each, and the possibility of a more systemic etiology for bilateral cataracts and a more local cause for unilateral infantile cataracts.

Our study has several strengths. The first is the size of our study. Because they are relatively rare events, infantile cataracts are challenging to study. By utilizing the multi-site, collaborative nature of the NBDPS, we were afforded the opportunity to study risk factors for infantile cataracts among a relatively large group of case-infants. Previous studies have suggested that etiologic heterogeneity may complicate epidemiologic analyses designed to identify risk factors for birth defects; thus, we took advantage of the careful classification of case-infants into etiologically and pathogenetically homogeneous case groups by the NBDPS, which includes a standardized method of case classification to classify case-infants into those with isolated cataracts and those with multiple congenital anomalies.¹⁸ In addition, we created even more homogeneous groups for analysis by both excluding case- and control-infants with a family history of infantile cataracts (thus focusing on unknown risk factors of infantile cataracts) and grouping case-infants by laterality.

Our study also had several limitations. Clinical data on case-infants are based on information abstracted from medical records, and specific information from the ophthalmologic examination on the morphologic structure, location and extent of the opacification was often not available. NBDPS classified cataracts into 3 types, anterior polar, other specified and not otherwise specified. The majority of cataracts were classified as not otherwise specified. In order to create more homogeneous groups for analysis, more complete data are needed on the type of cataract. Also, for future studies, it might be more appropriate to exclude anterior polar cataracts as they are not usually visually significant.² We were unable to do this in our study because some sites might have been better at documenting types of cataracts, resulting in exclusion of more case-infants from certain study sites, potentially introducing a selection bias. Also, we may have inadvertently excluded eligible case-infants from our study because only infants diagnosed with cataracts by an ophthalmologist within the first twelve months of life were included. This limitation has been noted in other studies⁸; one study based in Australia noted that 56% of infantile cataracts of unknown etiology were diagnosed by one year of age⁴ and another study based in the United Kingdom found that 33% of cases of infantile cataracts were diagnosed after one year of age,³⁴ but as far as we are aware the magnitude of this limitation has not been reported in the United States. Another limitation is that NBDPS relies heavily on mothers' ability to recall exposures, and this can result in either nondifferential or differential misclassification of certain exposures.³⁵ And, due to the small number of cases, we were not able to explore effect modification.

In conclusion, the findings of this study and others suggest that bilateral and unilateral infantile cataracts have different risk factors and should be examined separately. Our findings may suggest some possible risk factors for examination in future studies. Future studies of cataracts that can more completely ascertain maternal infection and its specific timing during pregnancy might provide important clues to etiology. Consideration of possible genetic risk factors will also be important in future studies. Given that cataracts are a major cause of childhood blindness worldwide, and that the majority of cases are of unknown etiology, it is important to identify risk factors for infantile cataracts so that strategies for their prevention can be instituted.

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Characteristics of Infantile Cataracts by the Presence or Absence of a Positive Family History of Infantile Cataracts, National Birth Defects Prevention Study, 2000–2004

Table 1

Characteristic	Total		Unilateral Cataracts		Bilateral Cataracts	
	n	%	n	%	n	%
Total	187		110	59	77	41
Positive Family History*	35		1		34	
Isolated cataract(s) alone	30	86	1	100	29	85
‡ Multiple major birth defects	5	14	0	0	5	15
No Family History*	152		109		43	
Isolated cataract(s) alone	137	90	104	95	33	77
‡ Multiple major birth defects	15	10	5	5	10	23

* Family History = Infants with a first-degree relative (parent or sibling) with infantile cataracts

‡ Multiple major birth defects defined as cataract(s) with at least one other major, unrelated birth defect

Effect Estimates for the Association between Unilateral Infantile Cataracts and Various Potential Risk Factors, National Birth Defects Prevention Study, 2000–2004

Table 2

Characteristic	Cases	Controls	Adjusted* Odds Ratio	95% C.I.
Birthweight				
VLBW (<1500g)	6	34	6.0	(2.2–16.3)
LBW (1500–2499g)	2	218	0.2	(0.03–1.4)
Normal (2500–3999g) (ref)	85	3522	1.0	---
Macrosomic (≥4000g)	14	415	1.4	(0.7–2.5)
Maternal Race Categories				
Non-Hispanic white (ref)	69	2437	1.0	---
Non-Hispanic black	16	474	1.3	(0.7–2.4)
Hispanic	19	965	0.9	(0.5–1.6)
Other	4	313	0.6	(0.2–1.6)
Maternal Age at Delivery				
<25 years old	35	1437	0.7	(0.4–1.2)
25–34 years old (ref)	58	2184	1.0	---
>34 years old	16	586	1.2	(0.7–2.1)
Maternal Education				
0–12 years (ref)	37	1739	1.0	---
>12 years	72	2405	1.3	(0.8–2.1)
Gravidity				
1	39	1215	1.6	(1.0–2.7)
2	32	1247	1.2	(0.7–1.9)
> 2 (ref)	38	1734	1.0	---
Respiratory illness during pregnancy				
No (ref)	61	1998	1.0	---
Yes	42	1994	0.6	(0.4–1.0)
UTI during pregnancy				
No (ref)	86	3454	1.0	---
Yes	20	707	1.1	(0.7–1.9)
Ibuprofen use during pregnancy				

Characteristic	Cases	Controls	Adjusted* Odds Ratio	95% C.I.
No (ref)	83	3402	1.0	---
Yes	26	777	1.1	(0.7–1.8)
Alcohol use during pregnancy				
No (ref)	73	3042	1.0	---
Yes	36	1099	1.2	(0.7–1.8)
Maternal Substance Abuse during pregnancy				
No (ref)	100	4008	1.0	---
Yes	8	143	2.1	(0.9–4.8)

C.I. = Confidence Interval, VLBW = very low birth weight, LBW = low birth weight, ref = reference, Other = including Asian/Pacific Islander, Native American/Alaskan Native and 'Other', UTI = urinary tract infection

* Adjusted for birthweight, maternal race, maternal age at delivery, maternal education, gravidity, respiratory illness during pregnancy, UTI during pregnancy, ibuprofen use during pregnancy, alcohol use during pregnancy, and substance abuse during pregnancy

Effect Estimates for the Association between Bilateral Infantile Cataracts and Various Potential Risk Factors, National Birth Defects Prevention Study, 2000–2004

Table 3

Characteristic	Cases	Controls	Adjusted* Odds Ratio	95% C.I.
Birthweight				
VLBW (<1500g)	4	34	13.2	(4.2–41.1)
LBW (1500–2499g)	6	218	3.3	(1.3–8.1)
Normal (2500–3999g) (ref)	30	3522	1.0	---
Macrosomic (≥4000g)	2	415	0.6	(0.1–2.6)
Maternal Race Categories				
Non-Hispanic white (ref)	21	2437	1.0	---
Non-Hispanic black	7	474	1.3	(0.5–3.4)
Hispanic	12	965	1.3	(0.6–3.0)
Other	3	313	1.2	(0.3–4.0)
Maternal Age at Delivery				
<25 years old	11	1437	0.5	(0.2–1.1)
25–34 years old (ref)	25	2184	1.0	---
>34 years old	7	586	1.2	(0.5–2.8)
Maternal Education				
0–12 years (ref)	21	1739	1.0	---
>12 years	21	2405	0.7	(0.3–1.5)
Gravidity				
1	14	1215	1.5	(0.7–3.3)
2	13	1247	1.4	(0.6–3.0)
> 2 (ref)	16	1734	1.0	---
Gestational Diabetes				
No (ref)	38	3918	1.0	---
Yes	5	260	1.3	(0.5–3.9)
UTI during pregnancy				
No (ref)	33	3454	1.0	---
Yes	10	707	1.7	(0.8–3.7)
Ibuprofen use during pregnancy				

Characteristic	Cases	Controls	Adjusted* Odds Ratio	95% C.I.
No (ref)	36	3402	1.0	---
Yes	6	777	0.8	(0.3–1.9)
Acetaminophen use during pregnancy				
No (ref)	16	1445	1.0	---
Yes	27	2745	0.9	(0.4–1.6)
Aspirin use during pregnancy				
No (ref)	39	4007	1.0	---
Yes	3	170	2.0	(0.6–6.8)

C.I. = Confidence Interval, VLBW = very low birth weight, LBW = low birth weight, ref = reference, Other = including Asian/Pacific Islander, Native American/Alaskan Native and 'Other', UTI = urinary tract infection

* Adjusted for birthweight, maternal race, maternal age at delivery, maternal education, gravidity, gestational diabetes, UTI during pregnancy, ibuprofen use during pregnancy, acetaminophen use during pregnancy, and aspirin use during pregnancy