The epidemiology of extrahepatic biliary atresia in New York State, 1983–98

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Summary

The aetiology of biliary atresia, the leading cause of neonatal extrahepatic jaundice and the main indication for liver transplantation in children, is unknown. Recent research has focused on an infectious aetiology and the development of viral models in animals. The few published epidemiological studies report conflicting results for seasonal, geographical, and racial variations in incidence. In this study, New York State (NYS) Congenital Malformations Registry data from 1983 to 1998 were compared with resident live birth certificate data. County of residence, birth date, gestational age, birthweight, gender, maternal race and maternal age were extracted from the birth certificate data. Isolated and sequence cases were combined for analysis. Observed and expected numbers of cases were calculated by NYS region.

Overall, 369 biliary atresia cases were reported in the 16-year study period, a rate of 0.85 [95% CI 0.76, 0.93] per 10,000 live births. Of these, 249 isolated/sequence cases were ascertained, a rate of 0.57 [95% CI 0.50, 0.64] per 10,000 live births. The rate ratio of biliary atresia in New York City (NYC) compared with other NYS was 2.19 [95% CI 1.69, 2.84]. Seasonal patterns varied by region with spring births at highest risk in NYC and September to November births at highest risk in other NYS. The rate ratio in black vs. white mothers was 1.94 [95% CI 1.48, 2.54]. Birthweight and gestational age were associated with biliary atresia with preterm low-birthweight infants at highest risk [RR 3.24, 95% CI 2.20, 4.76]. The association of isolated/sequence biliary atresia with season, preterm birth, and low birthweight in our study supports an infectious disease hypothesis.

Introduction

Biliary atresia is the leading cause of extrahepatic obstructive jaundice in neonates and the leading indication for liver transplantation in children.\(^1\) Two hypothesised forms of the disease have been described.\(^1–3\) The embryonic form is characterised by early onset of neonatal cholestasis, lack of a jaundice-free interval after physiological jaundice, lack of bile duct remnants, and associated congenital anomalies. The perinatal or acquired form, characterised by a later onset, bile duct remnants, and lack of associated anomalies, is thought to be caused by an infectious agent or environmental toxin.\(^1\) Recent laboratory research has focused on an infectious aetiology, and viral models have been developed in animals.\(^5–31\) The viral suspects include cytomegalovirus,\(^5–11\) reovirus type 3,\(^12–23\) and rotavirus A-C.\(^24–31\)

Only a few epidemiological studies of biliary atresia have been published.\(^32–40\) In these studies, conflicting results for seasonal and geographical variations in incidence have been reported. In addition, the association of biliary atresia with race and low birthweight is not clear. To explore further these seasonal and geographical differences in the incidence of the perinatal form of biliary atresia, 16 years of live birth data from a large population-based registry were analysed in this study.
Methods

Data sources and study population

The New York State Congenital Malformations Registry is one of the largest statewide, population-based birth defects registries in the United States. New York hospitals and physicians are required by law to report to the Registry malformations not resulting from birth trauma in children under 2 years of age who are born in or reside in New York. Individual cases are reported on forms provided by the New York State Department of Health. Case information, including the narrative description of the malformation, is reviewed and coded. The case is matched to existing Registry reports for possible duplicates.

Records of biliary atresia cases were extracted from the Registry for the years 1983 to 1998. Cases were matched to New York State live birth certificate records by year of birth and birth certificate number. Resident live birth certificate data for the same years were used to represent the population at risk.

Case classification

Biliary atresia cases were selected from the Registry using the International Classification of Diseases, Ninth Revision (ICD9) code 751.61 for the 1983 to 1991 data, and the modified British Paediatric Association (BPA) code 751.65 was used for the 1992 to 1998 data. Biliary atresia was represented by one specific code in each scheme. The embryonic form of the disease is associated with multiple anomalies, whereas the perinatal form is not. To distinguish between the two hypothesised forms of the disease, records of the biliary atresia cases were reviewed to separate cases with multiple malformations or syndromes from the perinatal analysis group. Cases without additional reported malformations or with a minor unrelated anomaly, such as umbilical hernia, were classified as isolated events. Cases with related hepatobiliary anomalies considered as sequelae of biliary atresia (e.g. disorders of bilirubin excretion) were classified as sequence events. Trisomies were categorised as syndromes. The remaining records of cases with additional major malformations were classified as multiple anomalies. Since it is hypothesised that the perinatal form of biliary atresia has an environmental aetiology, the isolated and sequence cases were combined to represent the perinatal form for the analyses.

Study variables

County of residence, date of birth, birthweight, gestational age in weeks, gender, maternal race, and maternal age were collected from the computerised birth certificate data files. County of residence was grouped into New York City and other New York State categories. Year and month of birth were created from date of birth. Month of conception was estimated using gestational age in weeks and date of birth. Month of birth was collapsed into four seasons: winter (December–February), spring (March–May), summer (June–August), and autumn (September–November). Birthweight was grouped as low birthweight (<2500 g) and normal birthweight (≥2500 g). Gestational age was categorised as preterm (<37 weeks) and term (≥37 weeks). To be comparable with Yoon et al., birthweight and gestational-age were used to create weight for gestational age categories as defined by the Centers for Disease Control and Prevention: preterm low birthweight, preterm normal birthweight, term low birthweight, and term normal birthweight. Maternal race was categorised as white, black, and other. Maternal age was grouped as <25, 25–34, ≥35 years.

Statistical analyses

Biliary atresia incidence rates with 95% confidence intervals [95% CI] were calculated for isolated/sequence cases. Observed and expected frequencies for county of residence, year of birth, and month of birth were calculated, assuming a constant incidence of disease. Chi-square tests were used to assess statistically significant variations. Three-year and 3-month moving average rates were calculated by region. The Walter and Elwood test for seasonality with a variable population at risk was used for months of birth and conception. Crude and multivariable Poisson regression analyses were performed and 95% CIs were calculated for region, season of birth, weight for gestational age, maternal race, maternal age, and gender categories. As ~46% of live births were to residents of New York City, an area that accounts for <1% of the total area of New York State, separate crude and multivariable Poisson regression analyses were performed for New York City and other New York State.

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Results

Study population characteristics and case ascertainment

For the 16-year study period, 4,365,940 resident live births were recorded in New York State. Table 1 shows the distribution of risk factors in the study population by region. A total of 369 biliary atresia cases was extracted from the Congenital Malformations Registry, a rate of 0.85 [95% CI 0.76, 0.93] per 10,000 live births. Of these, 112 cases were associated with multiple anomalies and eight were associated with syndromes. Two hundred and forty-nine (67%) of the cases were classified as isolated or sequence events, a rate of 0.57 [95% CI 0.50, 0.64] per 10,000 live births. The rate of isolated/sequence biliary atresia in New York State did not vary significantly by year during the 16-year study period.

Geographical and seasonal variation

Forty-six per cent of the New York State live births during the study period were born to mothers residing in New York City (Table 1), and 161 (65%) of the isolated/sequence biliary atresia cases were from this region. Table 2 shows that the rate ratio for New York City compared with the rest of New York State was 2.19 [95% CI 1.69, 2.84]. After controlling for weight for gestational age, season of birth, maternal race, and gender with multivariable Poisson regression analysis, the rate ratio remained significant at 1.83 [95% CI 1.38, 2.42].

The yearly rate of biliary atresia in New York City births did not vary significantly over the 16-year period. However, the biliary atresia rate in the other New York State region varied significantly over the study period with a \( P \)-value of 0.004. Figure 1 shows the smoothed rates over time. At the beginning of the study period, the difference in rates between the
<table>
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<th>Variable</th>
<th>Total New York State</th>
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<th>Other New York State</th>
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<tr>
<td></td>
<td>n</td>
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<td>aRR [95% CI]</td>
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<sup>a</sup>Winter, December–February; Spring, March–May; Summer, June–August; Autumn, September–November.
<sup>b</sup>WGA, weight for gestational age; Preterm, <37 weeks; Term, ≥37 weeks; LBW, <2500 g; NBW, ≥2500 g.
RR, rate ratio; aRR, adjusted rate ratio.
regions was greater than at the end of the study period. The difference was primarily because of an increase in the number of reported cases from upstate counties. The rates in the Long Island counties did not vary significantly during the time frame.

The analyses of season of birth presented in Table 2 and the plot of 3-month moving average rates by months of birth and conception presented in Fig. 2 show a difference in the seasonal pattern of biliary atresia by region. The New York City biliary atresia rate peaked in March births (1.41 per 10 000 live births), while the other New York State rate peaked in October births [0.81 per 10 000 live births]. The seasonal pattern is stronger in the other New York State region than in the New York City region with 43.2% of other New York State biliary atresia births occurring in the September–November period. Chi-square analysis of cases by month of birth resulted in $P$-values of 0.579 and 0.008 for New York City and other New York State, respectively. Using the methods of Walter and Elwood on the New York City month of birth data, the $P$-value for the chi-square statistic for centre of gravity was not significant at 0.441. For month of birth in other New York State, the $P$-value for the chi-square statistic for
centre of gravity was significant at <0.001 with a goodness of fit $P$-value of 0.233, suggesting a poor fit to the simple harmonic curve.

To control for the effect of preterm delivery, the methods of Walter and Elwood were applied to the estimated month of conception data (not shown). In the New York City data, the $P$-value for the chi-square statistic for centre of gravity was borderline significant at 0.057. The $P$-value for the chi-square goodness of fit test was 0.402, suggesting a moderate fit to a simple harmonic curve. Using the same method on the other New York State region sample, the $P$-value for the chi-square statistic for centre of gravity was significant at 0.004 for month of conception, and the $P$-value for the chi-square goodness of fit test demonstrates a moderate fit to the simple harmonic curve at 0.410.

**Weight for gestational age, race, gender, and maternal age**

Table 2 shows the crude and adjusted rate ratios by weight for gestational age. In New York State overall, preterm low-birthweight infants were at highest risk with an adjusted rate ratio of 2.92 [95% CI 1.94, 4.24] compared with term normal birthweight infants. In the crude analysis of race, infants of black mothers in New York State were at highest risk with a rate ratio of 1.94 [95% CI 1.48, 2.54] when compared with infants of white mothers, but the rate ratio is reduced to 1.40 [95% CI 1.04, 1.88] in the adjusted analysis (Table 2). Infants of mothers of other races were also at a significantly higher risk in the unadjusted analysis, but the results were no longer significant in the adjusted analysis. Infant gender and maternal age were not significant risk factors in either analysis.

**Discussion**

**Case classification and incidence**

The incidence of isolated/sequence cases per 10 000 live births in our study, 0.57 [95% CI 0.50, 0.64], is similar to the incidences found in the two population-based studies that restricted their analyses to isolated/sequence cases, 0.63 [95% CI 0.45, 0.81] in Atlanta and 0.47 [95% CI 0.43, 0.51] in France. The isolated/sequence cases represented 67% of the total cases of biliary atresia during the 16-year study period. The percentage is lower than the 86% found in a metropolitan Atlanta study and the 92% reported from France. However, Schweizer reported that the perinatal form accounted for approximately 65% of all cases in a series of surgical patients.

**Geographical and seasonal variation**

Conflicting results about geographical variation in biliary atresia incidence exist in the epidemiological literature. A population-based study in Victoria, Australia reported a significant time-space distribution in urban cases, while a hospital-based study in north Texas found a significantly higher incidence in rural areas compared with urban areas. French territories had significantly higher rates than France. On the other hand, no significant geographical variations were shown in population-based studies in metropolitan France, Atlanta, or the Netherlands. In our study, a twofold difference in rates was seen in New York City infants compared with infants born elsewhere in the state, but the regional difference became smaller near the end of the study period.

Due to the passive reporting system in New York State, case ascertainment may have varied by region and time. New York City area hospitals are known to under-report anomalies which would make our finding an underestimate of the rate in the New York City infants. The increase in reporting from the upstate hospitals during the study period may reflect an under-reporting of biliary atresia cases by the less experienced medical records staff of the upstate hospitals in the earlier years and an increase in case ascertainment in the later years resulting from audits of the Registry with hospitalisation data. To improve case ascertainment with limited resources, the Registry has been auditing the completeness of reported malformations since 1993 by comparing the data with the malformations reported to the Statewide Planning and Research Cooperative System (SPARCS), a mandatory hospital inpatient and ambulatory surgery database reported to be 99% comprehensive. Because surgical intervention is required within the first months of life, infants with biliary atresia are seen in the hospital and are likely to be reported to both SPARCS and the Congenital Malformations Registry. In 1992, there was a change in the coding scheme from ICD9 codes to BPA codes. However, since biliary atresia is represented by one specific code in each scheme, case ascertainment should not have been affected.

If the regional differences were not due to reporting artifacts, the disease variation by maternal residence...
may be explained by regional differences in population density, environmental, or socio-economic factors. To protect confidentiality, the Registry data were provided to us at the county level. A street address or ZIP code-level analysis would have allowed us to perform a better time-space analysis including neighbourhood-level population density, socio-economic, and environmental variables.

The literature also reports conflicting results for seasonal variation in incidence of biliary atresia. A significantly higher number of cases was seen in the September to November months in north Texas. Significant seasonal clustering in December to March was found in metropolitan Atlanta using an active-surveillance, population-based registry. In Sweden, cases were unevenly distributed across birth months with peaks in March and November births. Contrary to these positive associations, seasonal variation in incidence was not supported in the studies in Hawaii, the Netherlands, Michigan, or metropolitan France. The seasonal patterns in New York State varied by region. The other New York State region showed a stronger seasonal effect than the New York City area. Months of birth and conception were both significant in other New York State region. Although biliary atresia cases may have been under-reported to the Registry, it is unlikely that the bias was differential by month of birth.

The seasonal variations seen in our study support an infectious aetiology. In other New York State, 43% of the cases were born in the September to November months in the 16-year period. The seasonal pattern in month of birth with a peak in the cooler months may be attributed to a viral aetiology. Rotavirus, one of the suspected viruses used to create animal models, causes peak infection in cooler months in the United States. Despite the weaker seasonal pattern in New York City, an infectious aetiology cannot be ruled out. There is a greater chance of coming into contact with an infectious agent in a densely populated area. As more than one viral agent has been used to create animal models in the laboratory, more than one infectious agent with different seasonal patterns may cause the disease.

Small sample sizes in the geographical and seasonality analyses were a limitation in our study and in all studies. When we restrict our comparisons to the two studies that attempted to limit analyses to the perinatal form of the disease, we are left with the studies from France and metropolitan Atlanta. The metropolitan Atlanta study, based on 49 cases in a 26-year period, found a non-significant threefold higher rate in Fulton County, the most densely populated county. The study also reported significant results for the test of Walter and Elwood for month of birth. Our regional variation and seasonality findings are consistent with the Atlanta study. However, according to Walter and Elwood, seasonality test results should be interpreted cautiously for samples smaller than 50. Our stratified analysis of seasonality by geographical region used samples of 161 and 88 for New York City and other New York State, respectively. The study in France, based on 385 cases in an 11-year period, had the most power to detect geographical and seasonal variations, and no significant results were demonstrated with the chi-square and Walter and Elwood tests for seasonality, Knox analysis of time and space-time clusters, nor the Spearman non-parametric correlation test to assess the association with urbanisation.

Weight for gestational age, race, gender, and maternal age

The Hawaii study, based on 20 cases, found a significant relationship between birthweight and biliary atresia. However, no association was seen with gestational age. The Victoria study, based on 55 cases, found no association with low birthweight. Using weight for gestational age groups, the metropolitan Atlanta study found term low-birthweight infants to be at the highest risk for disease. Since the aetiology of biliary atresia is poorly understood, it is not clear if term low-birthweight infants are more susceptible to biliary atresia or if term low birthweight is a result of the disease. Our results, based on a larger sample, found significant associations with low birthweight and preterm birth.

Infants of Chinese fathers in Hawaii had biliary atresia rates five times higher than infants of Caucasian fathers. In the Atlanta study, black infants were at highest risk in the unadjusted analysis. Our analysis showed black race was still a significant risk factor for biliary atresia even after controlling for geographical region and weight for gestational age. Maternal race, as reported on the birth certificate, may be a proxy for population density, environmental exposures, or other socio-economic factors. As in other major malformations, infants of black mothers in New York State are at higher risk for biliary atresia than those of white mothers. The sample was not large enough to explore further the relationship with race.
Our non-significant findings for gender are in agreement with other studies that reported results for gender. The studies in Hawaii and Victoria showed an association of biliary atresia with young maternal age. As in Atlanta, the rate ratios for maternal age groups were not significant in the New York State data.

Conclusion

Much of the recent laboratory research of biliary atresia has investigated the viral association in humans and animals, and the pathological findings in biliary atresia support an infectious aetiology. The association of isolated/sequence biliary atresia with season, preterm birth, and low birthweight in our study supports an infectious disease hypothesis. The regional variation should be further explored to determine if the differences are due to reporting artifacts or true geographical variations.

References


