Clinical Course of Recurrent Respiratory Papillomatosis in Danish Children

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Objective: To evaluate the clinical course of juvenile-onset recurrent respiratory papillomatosis (RP) with respect to age, disease duration, and maternal condylomas.

Design: Inception cohort study.

Setting: All ear, nose, and throat departments in public Danish hospitals.

Patients: Fifty-seven Danish children diagnosed with RP and born between 1974 and 1993 were observed for an average of 14 years after diagnosis.

Main Outcome Measure: Removal of respiratory papillomas by knife biopsy, laser surgery, or cryotherapy.

Results: Children younger than 5 years diagnosed with RP underwent an average of 4.1 surgeries in the first year of disease, the highest rate among all our patients. The overall surgery rate decreased over time after initial diagnosis but remained significantly higher for children with a younger age of onset for the first 4 years of disease ($p<.001$) and for children with a maternal history of condylomas in pregnancy for years 4 to 10 of the disease ($p<.001$). We also observed an independent and statistically significant ($p<.001$) decreasing surgery rate with increasing age and time from initial diagnosis. The trend for children with recurrent disease was a decreasing rate of surgical procedures (28 of 42 patients with recurrent disease); however, a third of patients (14/42) demonstrated a constant or increasing rate of surgical procedures over time.

Conclusions: The clinical course of RP is characterized by a high frequency of surgeries soon after diagnosis that diminishes over time and with increasing age. Additional studies are warranted to identify factors associated with cases that do not conform to the usual disease course.

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UVENILE-ONSET RECURRENT RESpiratory papillomatosis (RP) is characterized by benign papillomas occurring at junctions of the squamous and ciliary epithelium, particularly in the larynx. The causative agent of RP is human papillomavirus (HPV), most commonly HPV-6 and HPV-11; these viruses also cause condylomas. The incidence of RP is low, but recurrence is very common. The morbidity in affected children can be significant, and death can occur in rare instances of complete airway obstruction. The clinical course of RP and the surgical experience of these patients has been described in several studies based on cases seen in large hospitals.

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To conduct a population-based study of the epidemiology and risk factors of juvenile-onset recurrent RP in Denmark, we identified all cases of RP occurring in Denmark over a 20-year period and recorded the history of surgeries. We reported that the risk of a child acquiring RP was 1 per 144 births when there was a maternal history of condyloma during pregnancy, 200-fold higher than that of a child without a maternal history of condyloma. We also found that 37% of the children with RP had a maternal history of condyloma in pregnancy. In the present study, we describe the clinical course of all children diagnosed with RP over a 20-year period and observed for an average of 14 years after initial diagnosis. These data allow for a comprehensive evaluation of disease course in children with respect to patient age and the presence of maternal condylomas during pregnancy and delivery.

STUDY POPULATION AND DESIGN

We evaluated all pathologically confirmed RP cases in children born in Denmark between...
1974 and 1993. Patients were observed from the time of initial diagnosis to January 2000, the end of the study period. All surgeries occurring during this period for each patient were recorded. Patients were observed for a median of 14.1 years after initial diagnosis (interquartile range, 10.0-17.3 years; maximum follow-up, 24.2 years). Only 1 child was observed for less than 3 years.

To identify RP cases, we contacted all Danish hospitals with an otorhinolaryngology department (N = 22). Each hospital provided a list of patients who were admitted between January 1974 and January 2000 with a discharge diagnosis of benign neoplasm of the larynx, trachea, bronchus, or lung. Discharge diagnoses were based on International Classification of Diseases, Eighth Revision (ICD-8) before 1994 (ICD-8 codes 508, 212, 231) and ICD-10 after 1994 (ICD-10 codes J38, D14, D38). Codes from ICD-9 were not implemented in Denmark. There was no ICD code exclusively for RP. Medical records of all patients identified from the lists and born between 1974 and 1993 were reviewed.

Diagnoses of RP were distinguished from those of other benign conditions of the larynx on the basis of the histopathologic report included in the medical record. Polyps and singer nodes were the most common conditions identified in the medical records. All children identified from the medical record review with 1 or more surgeries to remove a histopathologically confirmed RP lesions were included in our study. We excluded cases with an adult onset, defined as occurring at age 17 years or older. The methods used to identify cases by medical-record review were identical to the methods used by Lindberg and Elbrond, who identified juvenile- and adult-onset RP cases occurring in a subpopulation in Denmark from 1963 to 1986. We independently identified all 17 patients described in this earlier study that matched the criteria for our study, and thereby demonstrated that our surveillance was excellent. The outcome of interest for all analyses was the surgical removal of a papilloma by knife biopsy, laser surgery, or cryotherapy. Information abstracted from the medical record for each case included the date of birth and the dates of all surgeries from the initial diagnosis to the end of study follow-up.

The primary variables of interest were age of onset, age at the time of each surgery, time from initial diagnosis, and presence of maternal condylomas at birth. Information about the presence of condylomas during pregnancy was obtained from the Danish Medical Birth Registry (which contains data on all live births and stillbirths to women living in Denmark and all infant deaths) and the Danish National Hospital Registry (which includes detailed information on all hospital admissions). Pregnant women diagnosed with condylomas during pregnancy were identified through confidential linking of these registries using each mother’s 10-digit Central Population Registry number, a unique identifier that has been provided to all Danish citizens since 1968. All Danish National Registries keep identifier information under the registry number, which enables the confidential linking of information from several registries. Diagnoses of condylomas were identified using discharge diagnoses according to ICD-8 code (the ICD-8 code for condylomata acuminata is 99.9). From the registries, we also obtained sociodemographic information on the mothers and newborns and details of the pregnancy and delivery such as method of delivery, gestational age, birth weight, and complications encountered during pregnancy and delivery.

Approvals were obtained from the Danish Data Surveillance Authority, the Scientific-Ethics Committees in Denmark, Johns Hopkins University, Bloomberg School of Public Health, and the Office for Human Research Protections of the US Department of Health and Human Services to access the national registries and the medical records of patients with RP.

**RESULTS**

In the 20-year period of observation there were 1.2 million births in Denmark. We identified 57 patients with RP, which corresponds to an incidence rate of 3.5 per 1 million person-years. The median age of onset was 5.5 years. Of these 57 patients, we identified 49 (17 with and 32 without a maternal history of condylomas) with complete information available for all surgical procedures; 42 of these had recurrent lesions. The 8 patients for whom we could not obtain complete data from the medical records were similar to those with complete follow-up data with respect to year of birth, year of diagnosis, and age at diagnosis (P > .05) and were excluded from further analyses.

The number of surgeries among patients with RP varied over a wide range, from only 1 surgery (7 patients) to more than 20 surgeries (4 patients); the median number of surgeries was 5 during the period of observation. Children with a maternal history of condylomas had an earlier median age of onset than children without such a history (4.3 years vs 5.9 years) and a similar median follow-up after diagnosis (14.1 years vs 14.6 years). Children with a maternal history of condylomas had a median of 12 admissions and 6 surgeries compared with 16 admissions and 5 surgeries for children without a maternal diagnosis. None of these differences reached statistical significance.

Surgeries that occurred during the study period for individual patients stratified by a maternal history of condylomas in pregnancy are plotted in Figure 1. The most striking observation was the high frequency of surgeries
in the first few years after initial diagnosis, which diminished with increasing age. Among children with a maternal history of condylomas (Figure 1A), 2 (12%) had 1 surgery during follow-up. Among children without a maternal history of condylomas in pregnancy (Figure 1B), 5 (16%) had 1 surgery during follow-up. There were no noticeable patterns with respect to age of onset or maternal presence of condylomas.

The surgery rate decreased over time after initial diagnosis (Figure 2). The highest surgery rate was observed for children diagnosed at younger than 5 years, who underwent 4.1 surgeries during the first year. Children with a maternal history of condylomas had a significantly higher surgery rate than children without such a history in years 4 to 10 after the initial diagnosis \( (P < .001) \). Children with an earlier age at diagnosis (ie, \( \leq 5 \) years) had a significantly higher surgery rate than those with an older age at diagnosis for the first 4 years after initial diagnosis \( (P < .001) \).

To separate the effects of the related scales of time from initial diagnosis and age, we examined the time scales concurrently (Table). The highest surgery rate of 2.9 surgeries per person-year was observed for children 5 years or younger who underwent 4.1 surgeries during the first year. Children with a maternal history of condylomas had a significantly higher surgery rate than children without such a history in years 4 to 10 after the initial diagnosis \( (P < .001) \). Children with an earlier age at diagnosis (ie, \( \leq 5 \) years) had a significantly higher surgery rate than those with an older age at diagnosis for the first 4 years after initial diagnosis \( (P < .001) \).

Figure 1. Follow-up for individual cases of juvenile-onset recurrent respiratory papillomatosis (N=49), represented by horizontal lines. Follow-up is depicted separately for children with a maternal history of condylomas (A; n=17) and children without such a history (B; n=32).

We identified all juvenile-onset recurrent RP cases diagnosed in Denmark over a 20-year period. For each pa-
tient, we identified all hospital admissions and surgeries from the medical records throughout the course of the disease to the end of study follow-up. The extended follow-up to a maximum of 24 years allowed for a comprehensive evaluation of the clinical course of RP. We found that the most common clinical course was a high surgery rate within the first 5 years after initial diagnosis of RP followed by a decreasing rate. The surgery rate decreased both over time after initial diagnosis and with increasing age. More frequent surgeries were observed for cases with an earlier age of onset and perhaps with a maternal history of condylomas in pregnancy.

Prior studies have also observed a decreased risk of surgery over time and with advancing age.\textsuperscript{7,10,13,20,21} Armstrong et al\textsuperscript{2} in the most recent and largest study were the only researchers to examine age and disease duration concurrently. They found that children with an age of onset younger than 3 years were 3.6 times more likely than children diagnosed at older ages to have more than 4 surgical procedures per year. They also reported a decreasing surgery rate during the first 5 years of disease and the highest surgery rates occurring in patients diagnosed before age 2 years. We observed an even more pronounced decline during the first 5 years of disease, particularly for patients diagnosed at younger ages. To our knowledge, the present study is the first to report surgery rates beyond 5 years of disease duration and to report surgery rates by patient age at the time of surgery.

The decreasing rate over time from initial diagnosis is consistent with the limited ability of the low-risk

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Age, y} & \multicolumn{2}{c|}{\textit{\leq}5.00} & \multicolumn{2}{c|}{5.01-10.00} & \multicolumn{2}{c|}{10.01-15.00} & \multicolumn{2}{c|}{\textgreater{}15.00} & \\
\hline
\textbf{PY} & Rate\textsuperscript{*} & Rate\textsuperscript{*} & PY & Rate\textsuperscript{*} & PY & Rate\textsuperscript{*} & PY & Rate\textsuperscript{*} & \\
\hline
\textless{}5.00 & 52.6 & 2.9 & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
5.01-10.00 & 119.3 & 1.2 & 49.6 & 0.3 & \ldots & \ldots & \ldots & \ldots & \ldots <.001 \\
10.01-15.00 & 59.1 & 0.8 & 100.4 & 0.3 & 43.5 & 0.1 & \ldots & \ldots & \ldots <.001 \\
\textgreater{}15.00 & 8.6 & 0.0 & 61.0 & 0.2 & 103.6 & 0.1 & 92.0 & 0.1 & 92.0 & 0.1 & .23 \\
\hline
\textit{P} value\textsuperscript{†} & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \\
\hline
\end{tabular}
\caption{Surgery Rate for Juvenile-Onset Recurrent Respiratory Papillomatosis Cases (\textit{n} = 49) by Attained Age and Year After Initial Diagnosis}
\end{table}

Abbreviation: PY, person-year.

\textsuperscript{*}Number of surgeries per PY.

\textsuperscript{†}\textit{P} value tests linear trend using Poisson distribution within category of time scale.
HPV types, HPV-6 and HPV-11, to persist in tissue compared with high-risk HPV types such as HPV-16, HPV-18, HPV-31, and HPV-45.22 Thus, the expression of RP may be a function of the survival time of HPV-6 and HPV-11 in the respiratory epithelium. Alternatively, a decreased surgery rate for those with the longest disease duration may reflect a change in the clinical management of patients over time. The increased frequency of surgeries among younger patients may represent a lower tolerance among clinicians for growing lesions in the more narrow airspace of younger children. Alternatively, the age effect may represent a more productive immune response to infection with HPV among older patients.

We also observed a higher surgery rate among patients with a maternal history of condylomas in pregnancy, which persisted up to 10 years after initial diagnosis. It is possible that a child with RP born to a mother with condyloma receives a higher dose of the virus than a child born to a mother with subclinical HPV infection. A possible limitation is that only hospitalized patients with condylomas were identified, which would result in an underestimation of the number of cases. However, there is little likelihood of this type of misclassification, since all women in our study gave birth in a hospital. The result of any misclassification that did occur would be to dilute the observed association between condylomas and RP.

Although previous studies have not examined the effect of maternal condylomas on disease course, there are some data regarding HPV type. Two HPV types, HPV-6 and HPV-11, are responsible for almost all cases of RP. The published literature reports HPV-6 to be more prevalent in condylomas,23-25 whereas these HPV types are found in more equal frequency in RP.9,26 This suggests that HPV-11 infection poses a greater risk of RP than does HPV-6 infection. Most studies have reported more aggressive disease among children infected with HPV-11,8,11,14,15; one study reported more aggressive disease among children with HPV-612; and 2 studies reported no association of clinical severity with HPV type.6,9 We have not yet studied this question in our Danish population.

The patients identified in the present study had a mean age of RP onset of 5.5 years (median, 5.5 years), which is older than previously reported estimates of the mean age of onset (3.3-5.2 years).6,7,9,12,13,27 However, 4 of these studies6,9,12,27 identified cases from a single hospital, which may not represent the disease experience of the population. Armstrong et al17 reported an estimate of 3.8 years in a large sample of patients with RP (N=399) enrolled over a 2-year period in a US-based national registry. The longer enrollment period of 20 years in our present study enabled the identification of all cases, including cases with shorter disease duration, thus reducing the likelihood of selection biases inherent to cross-sectional studies or follow-up studies with a shorter enrollment period. Our estimate is most consistent with the highest estimate of 5.2, reported by Lindeberg and Elbrond13 who used similar methods in a subpopulation of Denmark. The older age of onset among patients in the present study and those of Lindeberg and Elbrond13 may reflect regional differences in the epidemiology of RP or more conservative clinical management of cases in Denmark.

CONCLUSIONS

In this study, we identified all cases of juvenile-onset recurrent RP in Denmark diagnosed in a 20-year period. We observed the disease course in patients for up to 25 years. The rate of recurrent surgeries for children with juvenile-onset recurrent respiratory papillomatosis (n=42) is shown in Figure 3. Each line represents the rate (ie, hazard obtained from survival models) of recurrent surgeries over time for an individual case depicted separately for decreasing rate (A; n=28), constant rate (B; n=6), and increasing rate (C; n=8). Seven cases without recurrent disease were excluded.
years, corresponding to 690 total person-years of follow-up. Furthermore, we had the unique opportunity to observe patients from the time of the initial diagnosis.

As illustrated in our report, the hallmark of RH is a high frequency of surgeries in the years just after diagnosis of disease, particularly for the youngest patients. Despite the steady decrease in the overall frequency of surgeries over time, we demonstrated the highly varied surgery experience over time among individuals. In addition to age and disease duration, we identified a maternal history of condylomas in pregnancy as a possible modifier of the rate of recurrent surgeries.

The trend for children with recurrent disease was a high rate of surgeries initially followed by a decreasing surgery rate over time. However, one third of all patients experienced a fixed or increasing surgery rate throughout their disease course; these patients were more likely delivered by cesarean section. However, given the large number of factors examined from the Danish registries, this finding needs confirmation in other settings.

The most important variables are likely to be the virus type and the child’s immune status. In particular, HPV-11 is suspected to be associated with more aggressive disease and should be examined further.

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