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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**METHODS**

**STUDY POPULATION AND DESIGN**

We evaluated all pathologically confirmed RP cases in children born in Denmark between 1974 and 1993 and observed for an average of 14 years after initial diagnosis. 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.

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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.

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The statistical methods consist of a grouped analysis to illustrate overall patterns in disease progression and an individual analysis to identify cases that deviate from the overall pattern. In the grouped analysis, we first calculated surgery rates per person-year defined by categories of disease duration (ie, years after initial diagnosis). The Fisher exact test was used to identify statistically significant ($P < .05$) differences by maternal condyloma status and age at diagnosis. Second, we calculated the surgery rate defined by categories of age at the time of each surgery and disease duration concurrently. For each category defined by disease duration (ie, 0-5, 5-10, 10-15, and >15 years after initial diagnosis), the presence of a linear trend by age was evaluated using Poisson regression. The third component of the grouped analysis was to evaluate linear trends by disease duration within categories of age using Poisson regression.

For the individual analysis, we first calculated the time from the initial diagnosis to each subsequent surgery for a particular patient. The number of observations for each patient was equal to the number of recurrent surgeries during the study period. Therefore, patients with 1 initial surgery and no recurrent surgeries did not contribute to this analysis. We constructed statistical models to examine the hazard (similar interpretation to rate) of recurrent surgeries over time for each patient. These models used survival procedures based on the Weibull model, which is capable of distinguishing between a decreasing, increasing, or constant rate of recurrent surgeries over time. Fisher exact tests were used to compare factors identified from the Danish National Registries between patients with a decreasing surgery rate and patients with an increasing or constant surgery rate.

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, ≤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 were 5 years or less from initial diagnosis. Keeping the disease duration fixed (ie, ≤5 years since the initial diagnosis), we found that the surgery rate decreased from 2.9 to 0.0 cases per person-year with increasing age, a significant trend ($P < .001$). An age effect was not observed for other categories of years since initial diagnosis. A decreasing surgery rate was also observed over time after initial diagnosis independent of age. The surgery rate decreased over time from 1.2 to 0.3 surgeries per person-year for children aged 5 to 10 years ($P < .001$) and from 0.8 to 0.1 surgeries per person-year for children aged 10 to 15 years ($P < .001$).

Despite the overall trends observed from the grouped analyses (see Table 1 and Figure 2), we observed individual differences in the clinical course of RP (Figure 1). We used statistical models to further summarize the surgical experience of individual patients. Figure 3 depicts the change in the rate of recurrent surgeries over time following the initial diagnosis in each patient. The 7 patients with only 1 surgery were excluded. Most patients (67%) demonstrated a typical high initial rate of surgery followed by an immediate decrease (Figure 3A). Six patients demonstrated a constant rate of surgery throughout follow-up (Figure 3B), and 8 patients had a lower initial rate of surgery followed by a sharp or gradual increase (Figure 3C). Compared with patients who had a decreasing rate of surgery over time, those with a constant or increasing surgery rate were more likely to have been delivered by cesarean section (4 patients [31%] vs 1 patient [4%]; $P = .03$), the only statistically significant finding among factors examined. Patients who had a constant or increasing surgery rate were also more likely to be male (10 patients [71%] vs 15 patients [54%]) and have a maternal diagnosis of condyloma (6 patients [43%] vs 9 patients [32%]) than those with a decreasing surgery rate, although these factors did not reach statistical significance.

**COMMENT**

We identified all juvenile-onset recurrent RP cases diagnosed in Denmark over a 20-year period. For each pa-
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. Armstrong et al 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

Figure 2. Change in surgery rate after initial diagnosis of juvenile-onset recurrent respiratory papillomatosis (N=49). Rate is stratified by maternal history of condylomas in pregnancy (A) and age at diagnosis (B). Asterisk indicates P<.05 for the difference between strata at the given duration of disease.

### Surgery Rate for Juvenile-Onset Recurrent Respiratory Papillomatosis Cases (n = 49) by Attained Age and Year After Initial Diagnosis

<table>
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<tr>
<th>Years After Initial Diagnosis</th>
<th>Age, y</th>
<th>PY</th>
<th>Rate*</th>
<th>PY</th>
<th>Rate*</th>
<th>PY</th>
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<th>PY</th>
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<td>49.6</td>
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<td>0.1</td>
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<td>0.1</td>
<td>.23</td>
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</table>

Abbreviation: PY, person-year.
*Number of surgeries per PY.
†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, which may not represent the disease experience of the population. Armstrong et al7 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 after initial diagnosis. 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 RP 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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REFERENCES