National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis

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Background: Juvenile-onset recurrent respiratory papillomatosis (JORRP) is an infrequent but debilitating disease. Because JORRP is uncommon, it has proven difficult for studies at single institutions to accurately evaluate its natural history.

Objective: To characterize the clinical spectrum of JORRP.

Design: Standardized retrospective and prospective medical record abstraction.

Setting: Twenty-two tertiary-care pediatric otolaryngology centers throughout the United States.

Patients: All patients with JORRP younger than 18 years seen between January 1, 1996, and March 31, 2002.

Main Outcome Measures: Demographics, age at diagnosis, anatomic sites of disease, longitudinal disease course, frequency of surgery, need for tracheotomy, and medication history.

Results: The registry includes 603 children. The mean age at diagnosis was 4.0 years. The children underwent a mean of 5.1 surgeries annually. Current age, rather than age at diagnosis, was the primary determinant of surgical frequency. The larynx was involved at the time of diagnosis in 96.1% of children, and 87.4% had only 1 anatomic site involved. Children with 1 site involved were significantly older at diagnosis (mean age, 3.9 years) than those with 2 sites (mean age, 2.9 years). Most (74.2%) had stable disease over time, 5.8% showed progression of papillomas to new sites, and 17.9% had no evidence of disease for at least 1 year. Children with disease progression were diagnosed at a significantly younger age than those who remained stable or became disease-free. Children who required tracheotomy were significantly more likely to have progressive disease.

Conclusions: The registry has established the clinical course of JORRP in a large sample representative of the United States. Young age was the most important determinant of disease severity (frequency of surgery, extent of disease at diagnosis, and progression of disease). Addressing questions of pathogenesis and disease course will require a revised data collection instrument and molecular analysis of tissues.


Recurrent respiratory papillomatosis (RRP) is characterized by repeated growth of warts in the larynx and other parts of the respiratory tract. Human papillomavirus (HPV), usually type 6 or 11, causes RRP. These HPV types are associated with anogenital condylomas and are considered at low risk for malignant transformation. Recurrent respiratory papillomatosis in pediatric age groups, usually referred to as juvenile-onset RRP (JORRP), is rare, with prevalence estimates of 1.7 to 2.6 per 100,000 children in the United States. Although rare, JORRP is the most common neoplasm of the upper airway in children. Juvenile-onset RRP may persist for many years, resulting in physical and emotional sequelae, and at least $110 million annually is spent on direct medical costs.

Understanding the epidemiologic characteristics of JORRP will provide researchers and clinicians better insight into controlling and ultimately preventing the disease. However, the low prevalence of JORRP limits the number of patients at any one institution, and many questions about the disease remain. Juvenile-onset RRP is most commonly diagnosed in children between 2 and 3 years of age. Hoarseness or voice changes are the usual initial manifestations. Less commonly, airway obstruction by papillomas results in respiratory stridor or acute respiratory distress as a presenting sign. Treatment is directed toward removing obstructing lesions rather than elimination of all...
diseased or infected tissue.\textsuperscript{7} Repeated treatment of recurrences may lead to web formation and irreversible damage to the vocal cords. Juvenile-onset RRP varies in severity, with some children requiring few treatments, while others undergo several surgeries a month. In most children, the disease remits, while in others it persists into adulthood.\textsuperscript{8,9} Studies have not shown consistent ethnic or socioeconomic associations with the occurrence of JORRP or with its early manifestations or clinical course.

In January 1997, the Centers for Disease Control and Prevention started a National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis to collect information on a sufficient number of patients to systematically evaluate the natural history of the illness. This is an analysis of registry information collected during 5 years of operation.

\section*{METHODS}

The human subjects committees of the Centers for Disease Control and Prevention and participating institutions approved the study protocol. Human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this study.

Details concerning management of the National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis have been published.\textsuperscript{10} Briefly, the registry includes information on all children younger than 18 years with RRP who received treatment at 22 participating tertiary-care medical centers throughout the United States. When the registry was initiated in January 1997, retrospective data were collected on all prevalent cases seen within the prior year. Incident cases were added at the time of diagnosis. Registry staff abstracted medical chart information from each visit related to RRP until the patients were lost to follow-up, transferred to another nonregistry medical center, or died. This analysis includes information tabulated through March 2002.

Data from the registry represent a cohort of children enrolled at different ages and followed up with repeated measurements for varying intervals. We estimated aggressiveness of disease based on frequency of surgery, need for tracheotomy, and anatomic extent of disease. We calculated mean annual surgery rates by standard methods.\textsuperscript{11}

Statistical analyses were performed using SYSTAT, version 9 (SPSS Inc, Chicago, Ill). Numbers may vary across analyses because of missing information (eg, age and ethnicity). We used the $\chi^2$ test to compare categorical data, the $t$ test or paired-sample $t$ test for normally distributed continuous data, and the Mann-Whitney statistic for non-normally distributed continuous data.

\section*{RESULTS}

The registry included data on 603 children from sites throughout the United States (\textbf{Figure 1}). The median age at diagnosis was 3.1 years (range, 1 month to 17 years; mean age, 4.0 years). Boys slightly outnumbered girls (304 and 299, respectively). Most patients (380 [63.0%]) were white, 171 (28.4%) were black, and the remainder were Native American (5 [0.8%]), Asian (5 [0.8%]), and other or unknown (42 [7.0%]). Ethnicity was reported for 367 (60.9%) of the patients; 57 (15.5%) were identified as Hispanic and 310 (84.5%) as white or black non-Hispanic. About half (280 [46.4%]) of the patients were covered by Medicaid.

The children's clinical course has been followed up for a median of 3.6 years (range, 9 months to 18 years;

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Number of patients at each center of the National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis.}
\end{figure}
Children underwent 2 to 179 (mean, 21.6; median, 13.0) lifetime surgical treatments for their disease. No important differences were noted concerning frequency of surgery when analyzed grouped on patient sex, ethnicity, or Medicaid coverage. The number of annual surgeries ranged from 0.4 to 21.5 (mean, 5.1; median, 4.3). Children who were diagnosed as having RRP before 4 years of age had significantly more annual surgeries than those diagnosed at an older age (Figure 2). Younger children also underwent significantly more surgeries each year (Figure 3). To explore possible interactions between age at diagnosis and age at surgery, we plotted age-specific surgical frequency for cohorts defined by age at diagnosis for all incident cases (Figure 4).

Age-at-diagnosis cohorts showed similar mean annual surgeries for each age-at-treatment time frame.

Information on extent of disease at diagnosis was available for 580 children (96.2%) (Table 1). Most (507 [87.4%]) had papillomas restricted to 1 site, usually the larynx (487 [84.0%]). Fifty-seven had disease in 2 sites, 15 had 3 sites involved, and 1 patient had 4 sites involved. Sex, ethnicity, and Medicaid coverage were not associated with extent of disease. Children with disease restricted to 1 site were significantly older at diagnosis (mean age, 3.9 years; median age, 3.0 years) than those with papillomas at 2 (mean age, 2.9 years; median age, 2.4 years) or 3 (mean age, 2.7 years; median age, 1.1 years) sites (P = .02, Mann-Whitney statistic). Those with dis-
ease in the larynx or above were significantly older at diagnosis (mean age, 4.6 years; median age, 3.3 years) than those with disease in the larynx or below (mean age, 2.1 years; median age, 1.7 years) (P = .009, Mann-Whitney statistic). Finally, among children with papillomas at 1 site, those with disease above the larynx were significantly older (mean age, 9.0 years; median age, 6.8 years) than those with disease in the larynx (mean age, 3.7 years; median age, 2.9 years) (P < .001, Mann-Whitney statistic).

Of the 469 children with sufficient information to estimate the clinical course, most (348 [74.2%]) were stable, with no change in the number of anatomic sites involved with papillomas; 27 (5.8%) had disease that progressed to additional anatomic sites, and 94 (20.0%) had disease that regressed, with fewer sites involved (Table 2). Of those whose disease regressed, 84 (89.4%) remained free of disease for at least 1 year. No differences in clinical course were noted for patient sex, ethnicity, or Medicaid coverage. One hundred seventy-one children (incident cases) were diagnosed with papillomas limited to the larynx between January 1, 1996, and March 31, 2002. Of these, children with disease progression were diagnosed at a significantly younger age than those who became disease-free or who had stable disease (Figure 5). Considering only incident cases controls for “survivor bias” and findings were similarly significant among all 487 children with disease limited to the larynx at diagnosis. Interestingly, data on the clinical course were available for 10 of the 20 children with papillomas only above the larynx at diagnosis. Two became disease-free, and 8 remained stable, with papillomas restricted to the original site.

Tracheotomy tended to be performed on younger children, but there was no statistically significant difference in the distributions of age at diagnosis between those who received (mean age, 3.2 years; median age, 1.8 years) and did not receive (mean age, 3.8 years; median age, 3.0 years) a tracheotomy. Sex, ethnicity, and Medicaid coverage were similar among children who required tracheotomy, there was no apparent association of disease progression with age, ethnicity, or Medicaid coverage.

The 12 children with tracheotomy whose disease progressed to involve additional anatomic sites underwent the procedure 7 days to 28.8 months (mean, 7.8 months; median, 3.1 months) before disease progression. The 33 children with tracheotomy whose RRP remained stable or regressed had been followed up a mean of 77 months (median, 59.3 months; range, 1.6-209.6 months) following the procedure, and 15 (42.9%) had cannulas in place at their last clinical evaluation. Although all subjects had surgical treatments, the registry also tabulated information concerning use of ancillary therapy (Table 4). Such data were available for 387 patients, and 184 (47.6%) had at least 1 course of therapy in addition to surgery. Interferon was used most frequently (in 77 [41.9%] of children receiving ancillary therapy). Interferon was given in various formula-
Interferon alfa-2b, generic interferon, interferon alfa-2a, and interferon alfa), in doses between 500,000 and 7,800,000 U (mean, 3,100,000 U; median, 3,000,000 U). Interferon was usually administered subcutaneously (80.1% of the time) and less often intramuscularly (10.6% of the time) or intralesionally (9.8% of the time). Fourteen children (7.6%) received acyclovir orally in doses between 50 and 400 mg (mean, 260 mg) once or twice daily. Thirteen (17.1%) were administered cidofovir intralesionally in doses between 0.19 and 21.5 mg (mean, 7.0 mg). Fifty-three children (28.8%) were documented as receiving various formulations of indole-3-carbinole as adjuvant therapy. Sixty-seven children (36.4%) underwent 2 different courses of ancillary therapy, and distributions of medications used were similar. Use of ancillary therapy was similar at the 22 registry sites, except for 1 that treated all patients enrolled with ancillary therapy. There were no striking differences in medications used at the different hospitals. In general, children receiving ancillary therapy had more frequent surgeries before therapy (mean annual surgeries, 6.3 vs 4.2; \( P < .001 \), Mann-Whitney statistic) and were diagnosed at a younger age (mean age, 2.4 vs 4.1 years; \( P < .001 \), Mann-Whitney statistic) than those who did not.

**Table 3. History of Tracheotomy and Clinical Course of Recurrent Respiratory Papillomatosis**

<table>
<thead>
<tr>
<th>Clinical Course†</th>
<th>No Tracheotomy</th>
<th>Tracheotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children enrolled in registry</td>
<td>No evidence of disease</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Regressed</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>324</td>
</tr>
<tr>
<td></td>
<td>Worse</td>
<td>15</td>
</tr>
<tr>
<td>Children with disease at diagnosis limited to the larynx</td>
<td>No evidence of disease</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>303</td>
</tr>
<tr>
<td></td>
<td>Worse</td>
<td>14</td>
</tr>
</tbody>
</table>

*Data are given as number and number (row percentage) of children.
†No evidence of disease indicates for at least 1 year; regressed, disease involved fewer sites than at diagnosis; stable, disease remained limited to original sites; and worse, disease progressed to involve more sites.

The National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis data from 603 children with a mean follow-up of 4.9 years give the most comprehensive picture to date of the epidemiologic characteristics and clinical course of JORRP. The registry documents the considerable morbidity associated with JORRP. The children had 10,361 surgical treatments, and the average enrollee underwent 5.1 surgeries annually. Previous studies have reported that early age at diagnosis was significantly associated with aggressive disease (defined by frequency of surgery). However, the cohort analysis we performed showed that current age, rather than age at diagnosis, was the primary determinant of surgical frequency. This most likely reflects that younger children.
have smaller airways and thus require more frequent surgeries to maintain patency, but changes in immune competence or viral load with increasing age cannot be excluded.

Our results agree with previous findings that JORRP usually involves the larynx. Our data representing a large closely observed cohort of children from the major tertiary-care centers throughout the United States documented a strong association between age at diagnosis and extent and progression of disease. There was a significant trend of decreasing age at diagnosis associated with increasing number of sites involved. More important, there was a significant association between younger age at diagnosis and papillomas occurring below the larynx. Almost 6% of the children had disease that progressed to adjacent anatomic regions. Young age at diagnosis was significantly associated with progression of disease in children with lesions restricted to the larynx at the time of diagnosis. Finally, our data also reflect that JORRP limited to sites above the larynx differs from that in the larynx and below. Children with lesions in the upper airway are significantly older and appear to manage the disease well, with no evidence of spread in our study.

The registry also confirmed that patients with JORRP who require tracheotomy are more likely to manifest progressive disease extending to new sites. The data did not permit resolution as to whether this shows merely the need to perform tracheotomy in children with severe progressive disease or an independent association between need for tracheotomy and subsequent progression of JORRP. Only a randomized prospective study could clarify this issue. Interestingly, age at diagnosis was not associated with need for tracheotomy. As with numbers of procedures, we restricted our analysis to children with RRP limited to the larynx at diagnosis (to reduce confounding). Our finding contrasts with previous studies showing that patients with JORRP requiring a tracheotomy are diagnosed at a younger age than those not requiring the procedure.

The registry has 2 important limitations with regard to the clinical course and extent of disease. First, the median follow-up was only 4.3 years. Second, the nature of the registry restricted the data we could collect, limiting our analysis of severity at diagnosis and clinical course involvement of general anatomic regions. We designed registry data collection forms to be amenable to completion by busy clinic staff by a medical chart review and to be minimally disruptive to clinic operations. We intended this to be a preliminary effort that would evolve.

Details of lesions within the larynx need to be collected and analyzed. Several staging and scoring systems have been proposed, but none have gained widespread acceptance among clinicians and researchers. In response to the need for detail and uniformity, a new staging system has been proposed by the developers of the most widely used severity scales. It includes a subjective functional assessment of clinical factors and an anatomic assessment of disease distribution. The functional and anatomic scores can be used in combination to estimate an individual patient’s clinical course and response to therapy. This staging system has been analyzed through a validation trial and has demonstrated excellent surgeon-to-surgeon reproducibility, with minimal variability in scoring of the same lesions. This system may be helpful in standardizing future documentation and expanding the usefulness of the registry.

Our analysis of the clinical course and severity of JORRP was also limited by the nature of the data ascertained by medical chart review. Human papilloma virus causes JORRP, and analysis of viral factors and host response to infection must be examined to explain clinical aspects of JORRP in more detail. Human papilloma virus types 6 and 11 cause most cases of JORRP, and HPV 11 is believed to portend a poor prognosis for remission. However, there is no consensus concerning the association between HPV type and clinical severity. Perhaps with the more efficient techniques of current polymerase chain reaction and the number of potential samples available in the registry, the issue of genomic differences in infecting viral DNA can be resolved.

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A complete listing of the principal investigators in the RRP Task Force was published previously (Arch Otolaryngol Head Neck Surg. 1999;125:743-748).

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REFERENCES


