Predictors of Remission in Juvenile-Onset Recurrent Respiratory Papillomatosis

Snehal Ruparelia, MPH; Elizabeth R. Unger, MD, PhD; Rosane Nisenbaum, PhD; Craig S. Derkay, MD; William C. Reeves, MD

Objective: To determine factors associated with remission of juvenile-onset recurrent respiratory papillomatosis (JORRP).

Design: Longitudinal study.

Setting: Twenty-two tertiary care centers located across the United States.

Study Participants and Methods: The study included 165 patients diagnosed as having JORRP between January 1, 1997, and December 31, 2000. Kaplan-Meier curves and Cox proportional hazards models were used to determine associations between predictors and remission.

Interventions: Surgical excision and drug therapy.

Main Outcome Measures: Remission of JORRP, defined as no surgical procedures for at least 1 year, as associated with age at diagnosis, drug therapy in the first year after diagnosis, number of surgical procedures in the first year after diagnosis, and number of anatomic sites of disease at diagnosis. Demographic factors (sex and race) and Medicaid status were also evaluated.

Results: Older age at diagnosis was positively associated with remission of JORRP (hazards ratio for every increase of 1 year in age, 1.13; 95% confidence interval, 1.03-1.23).

Conclusions: Younger children were found to have persistent disease and often underwent an increased number of surgical procedures in the first year after diagnosis of JORRP. Sex and race were not important factors in determining remission.


Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare chronic disease that is diagnosed between birth and adolescence and caused by infection with human papillomavirus (HPV). Repeated growth of papillomas or benign tumors, usually in the larynx and upper respiratory tract, characterizes JORRP and may obstruct the airway, causing hoarseness, difficulty in breathing, abnormal cry, or voice change. JORRP results in substantial childhood morbidity.

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Juvenile-onset recurrent respiratory papillomatosis often runs a prolonged and variable course requiring multiple surgical procedures, which may be supplemented by drug therapy. Clinical remission from the disease does not require eradication of its causal agent. Rather, HPV may persist silently in normal tissue unless it is reactivated by epithelial trauma or a compromised immune system. Some cases remit spontaneously, while others endure through adulthood.

The factors that determine outcome remain unknown, although differences in HPV type and host immune factors play a significant role. Human papillomavirus types 6 and 11 are most commonly associated with JORRP. Furthermore, some studies have suggested that HPV type 11 causes more severe disease. There has been discussion that JORRP regresses with the onset of puberty, but recent data do not support this hypothesis. Remission appears to be more likely in children whose disease is diagnosed when they are between the ages of 6 and 10 years and when warts are confined to 1 anatomical site.

Previous studies from single institutions have examined risk factors for severe and clinically aggressive disease. How-
Demographic and Clinical Characteristics of 165 Patients With Juvenile-Onset Recurrent Respiratory Papillomatosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients With Remission/Total</th>
<th>% Remitting</th>
<th>Unadjusted Hazards Ratio (95% Confidence Interval)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Sex*</td>
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</tr>
<tr>
<td>Male</td>
<td>16/79</td>
<td>20.3</td>
<td>1.0</td>
<td>.93</td>
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<td>20/86</td>
<td>23.8</td>
<td>1.03 (0.53-1.99)</td>
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<tr>
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<td>25.5</td>
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<td>7/48</td>
<td>14.6</td>
<td>0.68 (0.29-1.57)</td>
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<td>Other</td>
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<td>0.95 (0.33-2.75)</td>
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<td>Medicaid†‡</td>
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<td>.33</td>
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<tr>
<td>Yes</td>
<td>16/65</td>
<td>24.6</td>
<td>0.71 (0.36-1.41)</td>
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<td>Drug therapy in first year after diagnosis</td>
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<td></td>
</tr>
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<td>No</td>
<td>27/137</td>
<td>19.7</td>
<td>1.0</td>
<td>.48</td>
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<tr>
<td>Yes</td>
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<td>32.1</td>
<td>1.31 (0.62-2.79)</td>
<td>.48</td>
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<td>Surgical procedures in first year after diagnosis‡</td>
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<td>≤4</td>
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<td>28.6</td>
<td>0.28 (0.11-0.73)</td>
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<td>1</td>
<td>31/141</td>
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<td>1.0</td>
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<tr>
<td>&gt;1</td>
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<td>21.7</td>
<td>0.94 (0.37-2.44)</td>
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<td>Age at diagnosis, y</td>
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<td>12/62</td>
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<td>1.0</td>
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<tr>
<td>&gt;3</td>
<td>23/103</td>
<td>22.3</td>
<td>1.71 (0.87-3.40)</td>
<td>.12</td>
</tr>
</tbody>
</table>

*Sex and Medicaid do not satisfy the proportional hazards assumption. †Medicaid status unknown for 15 patients. ‡Forty-seven patients were unavailable for follow-up during their first year in the study.

However, few studies examining factors associated with remission of JORRP have been published, which may reflect the relatively limited number of patients seen at individual institutions. The present study not only defines a standard for disease remission but also examines associations between clinical and demographic factors and remission in 165 children with newly diagnosed JORRP from 22 tertiary care centers located throughout the United States.

METHODS

SUBJECTS

The national registry for JORRP has been described in detail in a previous report. In brief, it is composed of medical records of children with JORRP who received treatment at 1 of 22 tertiary care centers throughout the United States. The registry includes data from 618 children whose disease was diagnosed between January 1, 1997, and September 18, 2002. We analyzed data from the 165 JORRP cases diagnosed between January 1, 1997, and December 31, 2000, and included information on disease status until June 13, 2002. This design allowed complete follow-up of at least 1 year. Patients who were unavailable for follow-up were treated as “censored” cases in the analysis.

Results

Remission was defined as the absence of surgical intervention for at least 1 year. Variables were used in their continuous scale as well as categorized according to previous studies of this cohort. For example, we classified the number of surgical procedures in the first year after diagnosis into 2 categories: 4 or fewer surgical procedures and more than 4 surgical procedures. Similarly, we categorized age at diagnosis as 3 years or younger and older than 3 years. Because of different lengths of follow-up and censoring, we used survival analysis methods to describe and test for the associations between time to disease remission and age at diagnosis, drug therapy in the first year after diagnosis, number of surgical procedures in the first year after diagnosis (defined only for those patients who had at least 1 year of follow-up), number of sites of disease, sex, race, and socioeconomic status (Medicaid). We calculated time to remission since diagnosis and used Kaplan-Meier curves to illustrate the unadjusted effect of each variable on disease remission. We assessed the proportional hazards assumption graphically by plotting log (−log) survival curves for each predictor category and verifying whether curves were parallel. We applied the Cox proportional hazards model to estimate unadjusted and adjusted hazards ratios and 93% confidence intervals (CIs). Analyses were performed using a commercially available software package (SAS Release 8.1; SAS Institute, Cary, NC).

We identified 165 JORRP cases over the study period. The median follow-up time for the cohort was 1.7 years (range, 0.01-4.61 years). The Table lists the demographic and clinical characteristics of the patients. Overall, 36 children (21.8%) experienced disease remission. There were not enough events to allow Kaplan-Meier estimation of the median time to remission. The maximum probability of remission was 44.2% at 3.6 years. Remission was significantly more common among children who underwent 4 or fewer surgical procedures in the year after diagnosis than those who underwent more than 4 procedures. Overall, 35.3% of the children who underwent 4 or fewer surgical procedures experienced remission, compared with 13.9% of those who underwent more than 4 procedures (Table). The Figure illustrates this effect, accounting for different durations of follow-up.

We determined that all variables satisfied the proportional hazards assumption, except sex and use of Medi-

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icaid because their log (−log) survival curves crossed. Age at diagnosis and number of surgical procedures in the first year after diagnosis were the only variables significantly associated with remission. As shown in the Table, age at diagnosis (considered as a categorical variable) was not significantly associated with remission. However, the adjusted hazards ratio for age at diagnosis, estimated by fitting a multivariate model that included age at diagnosis as a continuous variable, was significant and equal to 1.13 (95% CI, 1.04 to 1.24; \(P = .54\)). The adjusted hazards ratios for more than 1 site of disease (1.17) (95% CI, 0.43 to 3.08; \(P = .74\)), drug therapy in the first year after diagnosis (1.27) (95% CI, 0.58 to 2.78; \(P = .54\)), and nonwhite race (0.73) (95% CI, 0.35 to 1.52; \(P = .40\)) were not significantly associated with remission. We did not include the number of surgical procedures in this model because 47 patients (28.4%) did not complete the first year of follow-up; therefore, we could not calculate number of surgical procedures in the first year. A separate multivariate model estimated the adjusted hazards ratio for number of surgical procedures greater than 4 as 0.25 (95% CI, 0.01 to 0.66; \(P = .005\)). The adjusted hazards ratios for more than 1 site of disease, drug therapy, nonwhite race, and age at diagnosis were 1.18 (95% CI, 0.45 to 3.08; \(P = .74\)), 1.68 (95% CI, 0.75 to 3.76; \(P = .21\)), 0.69 (95% CI, 0.33 to 1.46; \(P = .33\)), and 1.14 (95% CI, 1.04 to 1.24; \(P = .004\)), respectively. Finally, we performed stratified analyses by sex and Medicaid use because these variables did not satisfy the proportional hazards model and could not be directly included in the model. Because Medicaid does not satisfy the proportional hazards assumption, the unadjusted hazards ratio of 0.71 for Medicaid use seems to be contradictory to the ratio of remission proportions among Medicaid users and nonusers (24.6% and 21.2%, respectively). The effect of age at diagnosis and number of surgical procedures remained unchanged.

### COMMENT

In this study of children with JORRP, we found that patient whose conditions were diagnosed at an older age were 1.13 times more likely than younger patients to experience disease remission (95% CI, 1.03 to 1.23). The hazards of remission increased by 1.13 for every 1 year in age at diagnosis. We used absence of surgical intervention for at least 1 year to define remission because it is an extremely stringent and unambiguous outcome and because we did not have a standard, validated instrument to measure remission based on clinical examination.

Previous studies have reported conflicting results concerning the age that best discriminates between aggressive and nonaggressive disease. A previous report from our registry found that children whose disease was diagnosed before 3 years had an increased frequency of surgical procedures. Furthermore, another study of reported cases from multiple centers reported that children younger than 3 years are 3.6 times more likely to undergo more than 4 surgical procedures per year and 2 times more likely to have more than 1 anatomical site affected by the disease. Perhaps these conflicting results arise as a consequence of dichotomizing the age variable in analyses rather than analyzing it as a continuous variable. As with remission, we used the number of surgical procedures as a proxy for disease severity because it is a stringent and unambiguous end point and because we did not have a standardized validated instrument to assess severity based on clinical evaluation. However, measures of health care use (eg, frequency of consultations and number of surgical procedures) are influenced by a variety of factors that may not reflect the true pathophysiological severity.

Repeated surgical excision of warts that obstruct the airway is necessary to correct respiratory distress in children with JORRP. Indeed, surgical excision may reactivate dormant HPV and hasten the recurrence of tumors. Conversely, patients who develop JORRP at younger ages may have more severe disease, which would result in more surgical procedures. Regardless of cause-effect relationships, frequency of surgery provides a strong indication of severity and aggressiveness of disease.

A previous analysis of data from the national registry defined severe disease as disease that requires more than 10 operations in a lifetime. Some studies have defined severity as disease that requires 10 operations in a lifetime with a frequency of more than 3 procedures per year, while others have defined aggressive disease as spread of papillomas below the larynx. The present study evaluated surgical information from the first year of disease because it reflects disease aggressiveness near the time of diagnosis and the associated probability of remission.

It was interesting to find that there was no significant difference in remission between patients who received drug therapy in the first year after diagnosis and patients who did not. However, about 10% of patients with JORRP receive drug therapy because of unusually aggressive disease, a figure that includes children who require more than 4 operations per year and those whose papillomas have spread below the larynx. As a result, drug therapy in the first year after diagnosis may not have been an accurate predictor of disease remission. Also, the numbers were small, which limited statistical power. Studies have examined the effects of certain drug therapies on the disease; however, determination of response to therapy is not consistent between studies. Further studies need to be carried out not only to address this issue but also to investigate differences in various drug therapies as they relate to disease remission. Also, prescription of drug therapy in the years after diagnosis (not just the first year) should be examined as it relates to remission.

Although we studied the relationship between remission and the number of anatomical sites involved by JORRP at diagnosis, we did not examine remission in terms of spread to other sites of the respiratory tract that may have occurred after diagnosis and throughout the clinical course of the disease. The number of anatomical sites infected with HPV at diagnosis provided an indication of disease severity at diagnosis but was not associated with disease regression in the present study. However, we would have been better able to explore this question if we had evaluated the spread of the virus to other anatomical sites with time. Spread to other sites can potentially make the disease more aggressive and difficult to treat, thus allowing the disease to progress.
Our data did not indicate any differences in remission between boys and girls, confirming the findings of previous studies. The same was true for socioeconomic status represented by Medicaid and the 3 racial groups studied, with equal proportions of each group experiencing recovery. Despite these findings, it is essential to study remission of disease within and between these racial groups while accounting for HPV type so that any differences, patterns, or trends in disease remission that might be attributable to the infecting HPV type can be explored. Without examining these potential differences, we cannot fully assert that there is no association between race and disease remission, especially given that a previous study found trends in disease persistence and racial group.9

Potential limitations of the present study must be addressed. Most important, the median follow-up time for all study participants was 1.7 years, which may have allowed us a glimpse of a subform of the disease rather than its complete clinical course. Furthermore, 41% of study participants could not be followed up throughout the surveillance period and were “censored” in the study’s analyses, which may have resulted in the misclassification of disease remission for some of these patients; it may have also weakened the statistical power of our findings by biasing them toward the null. Finally, our study did not consider HPV type in the analyses, and it is known that infecting viral DNA (types 6 and 11) plays a significant role in the aggressiveness and severity of JORRP and, ultimately, in its remission.

This is the first study, to our knowledge, to address remission of a rare disease in terms of known risk factors by using survival data and a relatively large sample size. The results provide important information on the probable course of JORRP that is applicable to the general population. The study was performed using information from patients with JORRP from cities across the United States, thus allowing a random sample and eliminating selection bias. Furthermore, Cox proportional hazards regression was an appropriate way to analyze our data regarding time to remission since diagnosis.

We conclude that further studies that incorporate the demographic and clinical factors examined by this study, as well as information on HPV type, specifics of drug therapy, and the role of the immune system, are needed to confirm our findings.

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REFERENCES