

Age of Sexual Life Onset as a Risk Factor for Reintervention in Pediatric Laryngeal Papillomatosis Patients

José Luis Treviño-González¹, Victor Samuel Zuñiga-Marquez², German A Soto-Galindo^{2*}, José Rosmal Cortés-Ponce² and Luis Garza-Montelongo²

¹Chief of Otolaryngology - Head and Neck Surgery Department, University Hospital, Monterrey, Mexico

²Otolaryngology - Head and Neck Surgery Department, University Hospital, Monterrey, Mexico

*Corresponding Author: José Rosmal Cortés Ponce, Otolaryngology - Head and Neck Surgery Department, University Hospital, Monterrey, Mexico.

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Abstract

Objective: To describe the sociodemographic, clinical, and surgical characteristics of pediatric patients who come for evaluation for laryngeal papillomatosis and associate them with their clinical outcomes.

Methods: Retrospective observational, longitudinal, and descriptive cohort. The medical records of patients who met the selection criteria were reviewed from January 2014 to August 2021.

Results: The average age at which these patients were diagnosed was 4.68 ± 3.26 years. From the diagnosis, it was found that the mean of interventions that they required later was 7.53 ± 8.28 throughout their lives and that the most predominant symptom in these patients was dysphonia, presenting in 14 (73.7%) subjects and that this same symptom it was found to be a factor associated with a greater number of interventions in these patients with a significance of $p = .04$. Unfortunately, the most frequent severities of dysplasia were moderate and severe with 8 (42%) and 7 (36%) patients respectively, which if we consider them together represent 78% of the studied population.

Conclusion: We found that the median average survival in the three reoperation periods was approximately 6 months. The risk factor that had the greatest statistical significance based on its association with reinterventions was the age of onset of sexual life.

The mean age at which these patients were diagnosed was 4.68 years. The mean interventions required was 7.53 throughout their lives and that the most predominant symptom in these patients was dysphonia. The most frequent severities of dysplasia were moderate and severe.

Keywords: Laryngeal Papillomatosis; Pediatric Otolaryngology; Human Papillomavirus; Recurrent Laryngeal Papillomatosis

Introduction

Recurrent laryngeal papillomatosis is a rare condition, but it can be life-threatening. It predominantly affects young people under 5 years of age and young adults. They are manifested by obstructive processes of the airways in its severe forms and in its mild forms

it manifests with dysphonia, being considered in typical cases the triad of dysphonia, stridor and respiratory distress.

It should be investigated, onset, aggravations, companions, fluctuations, current voice limitations and exacerbations. Papillomatosis leads to a course of intense recurrences, a more aggravated

condition in the juvenile presentation and more associated with serotype 11 than in comparison with the rest [1,2].

The prevalence of recurrence in children is such that Derkay established a scale to predict the time that will elapse before the next surgery, where he establishes that each subsite shortens the future procedure by 4 days; patients with 20 points or more will require a resection an average period of 120 days earlier than those with less than 20 points; aphonia, dyspnea and stridor are the symptoms that most shorten the interval between surgeries [3,4].

Laryngeal papillomatosis is an intracellular human papillomavirus (HPV) infection in the basal lamina of the epithelium, for which it is not possible to completely eradicate it with the methods used so far (surgical excision, application of medications), therefore there will be a relapse with the presence of lesions that obstruct the upper airway. So far, it has not been studied in depth what factors influence the time of recurrence, apart from age and viral serotype, so it is also necessary to consider the effect of the type of treatment, other comorbidities, site of injury or application HPV vaccine [5].

Currently there is little updated information on the clinical, sociodemographic, and surgical characteristics of this disease in our region, so the purpose of this study is to describe and identify clinical and sociodemographic characteristics of recurrent laryngeal papillomatosis patients and associate them with clinical outcomes.

Material and Methods

This is an observational, retrospective, longitudinal study of a retrospective cohort. In the present study, the records of pediatric patients diagnosed with laryngeal papillomatosis at a tertiary referral public hospital in the period from January 2014 to August 2021.

The sampling was carried out as consecutive cases by retrospectively reviewing the files.

The inclusion criteria were children under 17 years of age with an endoscopic and histopathological diagnosis of laryngeal papillomatosis. Subjects over 18 years of age, incomplete records, and patients with previous treatments before their referral to our center were excluded.

It was decided to use non-parametric tests such as Mann Whitney's U to search for associations between variables. The numerical and categorical variables will be compared using hypothesis tests.

To perform the statistical analysis of the variables socioeconomic status and locality of the patients, the following classifications were applied. For socioeconomic status, quartiles 25, 50 and 75 were obtained to separate the population into different groups and facilitate their use. For the locality, we rely on a publication by ECLAC to define whether the subject resides in an urban or rural area, taking as a cut-off point a population greater than or equal to 2,500 inhabitants, which would indicate that it is an urban area [6].

After performing the descriptive statistics, Kaplan Meier survival analyzes were performed for the three reintervention periods that were captured in the database. That is, this analysis was performed at 3 time points: between the first and second surgery; between the second and third surgery; between the third and fourth surgery. Subsequently, cox regressions were performed for the covariates IVSA, socioeconomic status, number of interventions and histological severity. This with the intention of finding an association between each covariate and the reintervention event. A value of $p < .05$ will be taken as the cut-off point for statistical significance. All statistical analyzes will be performed in the SPSS version 25 statistical package (IBM, Armonk, NY, USA) for Mac OS.

Results

There were 19 patients included in the study. It was found that all of them were first-born and that all the siblings that followed them did not suffer from the disease. The mean age at which these patients were diagnosed was 4.68 ± 3.26 years. From the diagnosis, it was found that the mean of interventions that subsequently required was 7.53 ± 8.28 and that the most predominant symptom in these patients was dysphonia, presenting in 14 (73.7%) subjects. The most frequent severities of dysplasia were moderate and severe with 8 (42%) and 7 (36%) patients respectively. The mean age of the mothers when they gave birth for these patients was 22.06 ± 5.53 and the mean age of the mothers at the start of sexual life was 16.33 ± 1.87 . The average time that elapsed for mild dysplasias to become moderate and those that were moderate to severe was 12.50 ± 16.26 and 15.20 ± 18.10 respectively. The rest of the clinical and demographic data are found in table 1.

Variables	Values	
Mother age at child's birth	22.06 ± 5.53	
Age of sexual initiation	16.33 ± 1.87	
Age at diagnosis	4.68 ± 3.26	
Number of surgical procedures	7.53 ± 8.28	
First to second procedure interval (months)	11.11 ± 13.64	
Second to third procedure interval (months)	5.29 ± 6.47	
Third to fourth procedure interval (months)	8.30 ± 10.94	
Progression from mild to moderate dysplasia interval (months)	12.50 ± 16.26	
Progression from moderate to severe dysplasia interval (months)	15.20 ± 18.10	
Sex, n (%)	Female	8 (42.1)
	Male	11 (57.9)
Income per month, n (%)	<200 USD	5 (26.3)
	200 - 300 USD	6 (31.6)
	301- 400 USD	2 (10.5)
	>400 USD	4 (21.1)
Mother education, n (%)	Primary	4 (21.1)
	Middle School	10 (52.6)
	High School	2 (10.5)
Father education, n (%)	Elementary	5 (26.3)
	Middle School	7 (36.8)
	High School	1 (5.3)
Way of birth, n (%)	Assisted natural childbirth	13 (68.4)
	C-section	1 (5.3)
Dysphagia, n (%)	Absent	17 (89.5)
	Present	1 (5.3)
Dysphonia, n (%)	Absent	4 (21.1)
	Present	14 (73.7)
Dyspnea, n (%)	Absent	8 (42.1)
	Present	10 (52.6)
Histological classification, n (%)	Insufficient sample	2 (10.5)
	Mild	2 (10.5)
	Moderate	8 (42.1)
	Severe	7 (36.8)
Progression from mild to moderate dysplasia, n (%)	No	17 (89.4)
	Yes	2 (10.5)
Progression from moderate to severe dysplasia, n (%)	No	14 (73.6)
	Yes	5 (26.3)
Tracheostomy, n (%)	No	16 (84.2)
	Yes	2 (10.5)

Table 1: Clinical and sociodemographic characteristics.

Using the Mann Whitney U test, an attempt was made to associate risk factors such as the mother’s age at birth, the patient’s age at diagnosis, and the age of sexual onset with the number of interventions required by the patients. None of the proposed factors was significant. However, the risk factor with the greatest significance ($p = .260$) was the diagnostic age of the patient, with an earlier age at diagnosis being observed in the group of interventions greater than or equal to 4.

Associations between the same risk factors with the severity of dysplasia were searched, without finding statistically significant associations. The risk factor that most closely approximated significance was the age of onset of active sexual life ($p = .097$).

An attempt was made to associate the factors of risk and clinical characteristics with the severity of dysplasia using chi-square tests, without finding any statistically significant data.

Finally, survival analyzes were performed for patients in question of the need for a reintervention. That is, the follow-up data of the patients were taken to see how long it took for them to need a surgical reintervention between their first and second surgery, between the second and third, and finally between the third and fourth surgery. In addition, cox tests were performed to map the influence of risk factors of interest in this reintervention outcome.

Figure 1 shows the survival curve of the patients captured between their first and second surgery. In this curve it can be seen that the median survival was 6 months, a period in which only 50% of the patients remained without presenting the event. After a year, only 14% were without presenting the event.

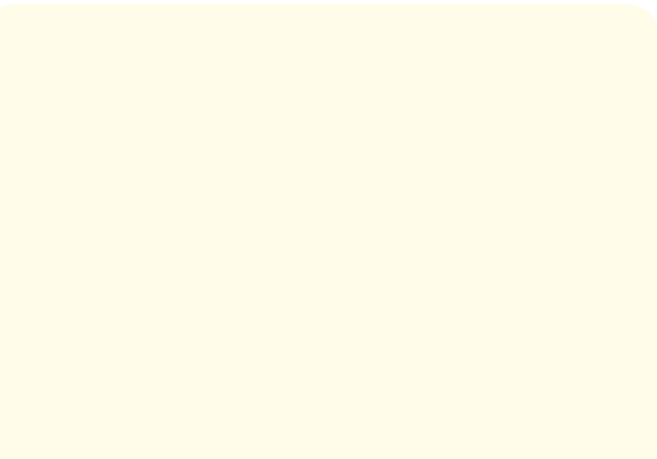


Figure 1: Survival analysis between first and second surgery.

Figure 2 shows the survival curve of the patients captured between their second and third surgery. In this curve, it can be seen that the median survival was 5 months, a period in which only 50% of the patients remained without presenting the event. At 6 months only 34% were exempt from the event and at one year only 17% of the population was without demonstrating the event.

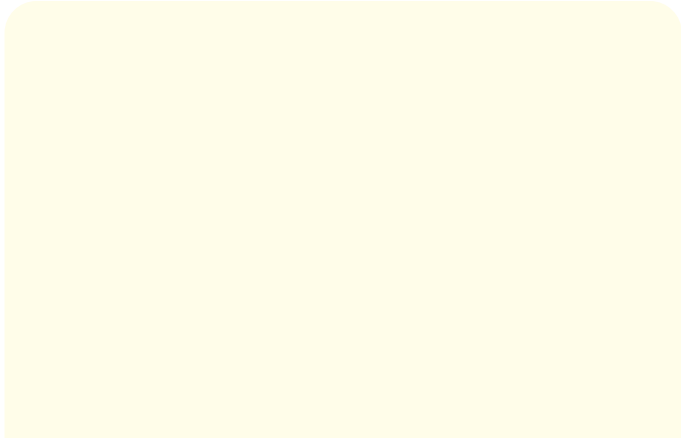


Figure 2: Survival analysis between second and third surgery.

The survival curve of the patients captured between their third and fourth surgery are shown in figure 3. In this curve it can be seen that the median survival was 7 months, a period in which only 50% of the patients remained without presenting the event. At 6 months, 60% were exempt from the event and at one year only 30% remained without presenting the observed event.

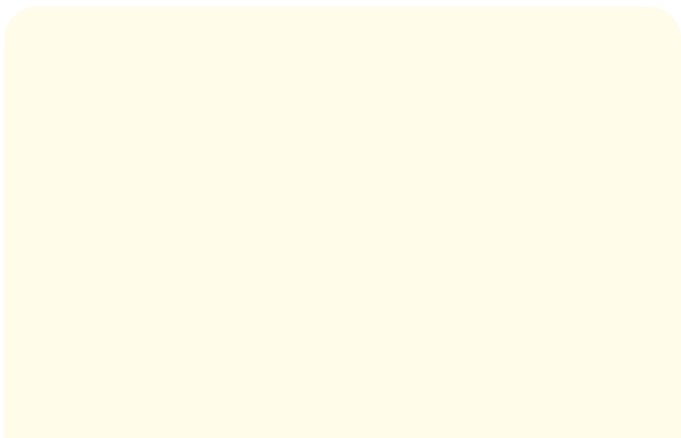


Figure 3: Survival analysis between third and fourth surgery.

Subsequently, cox regressions were performed to assess the association between the covariates and the outcome to be evaluated.

Figure 4 shows that the age sexual life initiation had a significance p of .06 with a risk ratio of .14 with a 95% CI ranging from .02 to 1.08 in terms of requiring a new procedure. In this regression, the older sexually initiated group was compared with the younger group. This shows that having 18 years or older when initiating sexual life confers a protective factor in the presence of the reintervention event. The median survival for the sexual initiation group older than 18 years was approximately 5 months and the group younger than 18 years was approximately 1 month.

Figure 4: Survival analysis by cox regression for covariate between first and second surgery.

After the regression analyzes, it was found that a subjects with mild dysplasia compared to the moderate and sever does not have a significant difference in terms of the risk of the occurrence of the event. The income groups were also analyzed and found no significant differences.

Discussion

The mean median survival in the three observation periods was found to be 6 months. Across the three periods, it is stated that age of sexual life initiation at an age over 18 years is a protective factor against the need for reoperation.

Regarding the severity of dysplasia, it was found that the severity of the pathology is indistinguishable from the need for reoperation. This can be explained given that the disease is highly recur-

rent regardless of its degree of dysplasia, however, in the literature it is verified that a more aggressive dysplasia requires a greater number of interventions. However, the data reported in this study are not conclusive as they lack statistical significance in most of the results.

It was also found that all the subjects with papillomatosis were first-born and that, if they had siblings after them, they did not present the disease. Being able to interpret that awareness is generated about this pathology after having occurred once and the appropriate preventive measures were applied so that it did not happen in the rest of the offspring.

It was shown that the average age of the mothers when they gave birth for these patients was 22.06 ± 5.53 years and the average age of the mothers at the beginning of sexual life was 16.33 ± 1.87 years. Unlike what is proposed in the literature, these factors could not be significantly associated with any of the outcomes established in this study; however, the age of sexual life initiation factor was found to be close to statistical significance on several occasions.

Another relevant feature to be noted in our study is that the first period of time required to go to the second surgery was the longest compared to the other two periods of time. Therefore, it may be relevant to explore in the future whether the reintervention period could be shortened with each intervention performed on patients.

In a longitudinal study, it was reported that patients who had papillomatosis and were less than 3 years old had a more aggressive pattern of the disease. However, in the present study, no significant association was found to support this fact that has been well studied over time. This may be due to the lack of power caused by a small sample size [7].

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In a systematic review it is commented that this pathology is known for its great recurrence despite the surgical therapeutic lines that are used. This is evident in almost all the patients since

the need for reoperation was presented in most of them. In the same way, it is mentioned in this study that maternal prevention through the HPV vaccine or timely treatment of the disease in the mother can prevent the appearance of the disease in the following children, something that is perceived in the study when noting that these Affected patients were first-born and were the only ones affected considering the rest of the siblings [2].

In another secondary study, our significant association regarding the symptom of dysphonia as an important indicator for the progress of the disease was reaffirmed. However, this study focuses more on the relevance of the recurrence characteristic of this disease and how this is limited in developing countries. Thus, indicating that communities with fewer economic resources have less opportunity to face the disease [8]. However, in our study no association was found between socioeconomic status or whether the type of locality, whether rural or urban, had any association with these outcomes. This may be due to the limitation of the study in terms of sample size and its sampling.

In another review focused on the preventive impact of the HPV vaccine, it is pointed out that this can considerably reduce the economic, physical, social and emotional costs related to this disease [9]. In our article, it was found that women who had an SAVI at an age over 18 years were associated with a protective factor against the need for reinterventions. Leaving in doubt whether this is due to the fact that prevention programs are merely focusing on the adult population and leaving aside the population under 18 years of age. However, there is another review in which it is commented that papillomatous variants in young adults tend to be more aggressive and quicker to recurrence compared to the population over 20 years of age [10]. This fully agrees with our study, it only indicates that the cut-off point for age can vary within a range of 2 years.

A systematic review indicates that natural delivery lasting more than 10 hours is a relevant risk factor for the transmission of the disease to the neonate. Notwithstanding this same study, it indicates that there is still doubt as to whether cesarean section provides any protective factor against the condition, since no conclusive information has been found [11].

Conclusion

The median average survival in the three reoperation periods was approximately 6 months. The risk factor that had the great-

est statistical significance based on its association with reinterventions was the age of onset of sexual life. The mean age at which these patients were diagnosed was 4.68 years. From the diagnosis, it was found that the mean of interventions that they required later was 7.53 throughout their lives and that the most predominant symptom in these patients was dysphonia, presenting in 73.7% subjects. The most frequent severities of dysplasia were moderate and severe in 42% and 36% respectively, which if we consider them together represent 78% of the studied population.

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