

Recurrent Respiratory Papillomatosis in Children. Some Clinical-epidemiological and Therapeutic Aspects

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Abstract

Introduction: Recurrent respiratory papillomatosis is a rare airway disease affecting children and adults, caused by papillomavirus infection.

Objective: To perform a clinical-epidemiological characterization of recurrent respiratory papillomatosis in pediatric patients and evaluate the evolution of these patients in the short and medium term.

Methods: An observational, longitudinal and prospective investigation was carried out in pediatric patients with the diagnosis of recurrent respiratory papillomatosis, attended in the Otolaryngology Service of the South Children's Hospital "Antonio María Béguez César" of Santiago de Cuba from January 1, 2010 to December 31, 2016.

Results: The patients included in the study represented 3.17% of total admissions, male patients predominated (60%), the mean age was 8.6 ± 4 years. There was a statistical association between the anatomical location of the lesions and the male sex, it was the oropharyngeal location (50%) and the laryngeal location (42.5%) that were the most observed, there was no statistical association between the location of the lesions and age. Transvaginal delivery was associated with the highest number of cases of recurrent respiratory papillomatosis (85%) and treatment with excision and interferon was associated with satisfactory evolution in 95.8%.

Conclusions: The clinical characteristics and epidemiologies of patients with recurrent respiratory papillomatosis of this casuistry do not differ from the global epidemiological context, being a rare observation entity, but not rare in pediatric services.

Keywords: Papillomavirus; Recurrent Papillomatosis; Transvaginal; Children

Introduction

Papillomaviruses are small viruses capable of causing malignant epithelial lesions, they are also the cause of a wide range of proliferative lesions of a benign nature [1].

Between 80 and 90% of the population will have contact at some point in their lives with papillomavirus (HPV) [2].

The infective mechanism is associated in most cases; to the participation of the individual in sexual practices of various kinds, however such infection can also be acquired by other routes of contagion. One of them is the transmission from mother to child, either during pregnancy or at the time of delivery [2].

There are more than 200 serotypes of the virus, 40 of them linked to infection in humans, with serotypes 16 and 18 being higher risk, and low risk 6 and 11. The infection can have a self-limiting course and be asymptomatic or evolve to oropharyngeal, cervical-uterine and rectal cancer, it can also manifest as genital warts and recurrent respiratory papillomatosis (PRR) [3].

PRR is the most frequent infantile laryngeal tumor, it has a bimodal incidence with characteristic clinical forms for each age group: the recurrent juvenile form in the group of children under 5 years, transmitted from mother to child during childbirth, which is characterized by being more aggressive and juvenile papillomatosis continues towards adulthood [3].

PRR is a rare airway disease that affects children and adults, has an unpredictable course and has been reported to be pulmonary extension and malignant transformation. Serotypes 6 and 11 most often cause respiratory lesions that can be located primarily in the larynx, although they may be present throughout the entire respiratory tract [4,5].

This disease has repercussions on those who suffer from it, their families and the health system due to its recurrent nature. It merits an urgent therapeutic behavior on the part of the otolaryngologist, elements that motivated us to carry out this research in order to carry out a clinical-epidemiological and therapeutic characterization of this problem; and evaluate the evolution of these patients in the short and medium term.

Methods

An observational, longitudinal and prospective research was carried out in pediatric patients with the diagnosis of recurrent

respiratory papillomatosis, attended at the Otolaryngology Service of the South Children's Hospital "Antonio María Béguez César" of Santiago de Cuba from January 1, 2010 to December 31, 2016, with the purpose of carrying out a clinical-epidemiological characterization of this problem and evaluating the evolution of these patients in the short and medium term.

The collection of information was carried out through anamnesis and physical examination, in addition to the data from the individual medical history, taking into account that all the children were admitted to the Otolaryngology Service of the institution and were followed up by external consultation once they had graduated.

The university consisted of 42 patients with the diagnosis of recurrent respiratory papillomatosis and the sample was made up of 40 children who met the inclusion criteria.

Inclusion criteria

- Patients up to 19 years of age admitted with a diagnosis of recurrent respiratory papillomatosis, confirmed by biopsy.
- Patients whose parents gave informed consent to be part of the study.

Exclusion criteria

- Patients up to 19 years of age admitted with a diagnosis of recurrent respiratory papillomatosis, not confirmed by biopsy.
- Patients whose parents did not give informed consent to be part of the study.

Se reviewed the hospital and outpatient medical records of children diagnosed with recurrent respiratory papillomatosis up to 19 years of age treated in the period of analysis.

A survey was carried out that included the following variables: age, sex, location of lesions, clinical evolution according to treatment, presence or absence of recurrences, type of treatment received, prenatal patients of vaginal infection and type of delivery.

The information obtained was processed in a computerized way using the SPSS version 10.0 package, which allowed the preparation of statistical tables that included absolute frequencies, percentages and the statistical association by the calculation of the p and RR value in the tables where it was possible to apply this validation, in which the results were presented.

Results

In the study period, a total of 1260 patients were admitted to the Otolaryngology service, 40 of them with a confirmed diagnosis of recurrent respiratory papillomatosis, representing 3.17%. Of these 6 cases respectively in the years 2010, 2011, 2015 and 2016, 4 in the years 2013 and 2014 and 8 in 2012. The average age was 8.6 ± 4 years. Se found a predominance of male patients with 24 children; figure that represented 60%.

When relating the anatomical location of the lesions caused by the virus papilloma with sex (Table 1), a statistical association was found between these variables ($p < 0.05$). In general, the oropharyngeal location was associated with the highest number of cases; 20 patients for 50%, followed by pharyngeal patients (42.5%), both locations were more relevant in the male sex with 60 and 58.8% respectively.

| Localization | Male | | Female | | N = 40 | |
|--------------|------|------|--------|------|--------|------|
| | No | % | No | % | No | % |
| Orophage | 12 | 60 | 8 | 40 | 20 | 50 |
| Laryngeal | 10 | 58,8 | 7 | 41,2 | 17 | 42,5 |
| Nasal | 2 | 66,7 | 1 | 33,3 | 3 | 7,5 |
| Total | 24 | 60 | 16 | 40 | 40 | 100 |

Table 1: Distribution of patients according to anatomical location of the lesions and their relationship with sex.

$p < 0,05$.

Table 2 refers to the anatomical location of the lesions caused by the human papillomavirus and their relationship with age, and although no statistical association was found between these variables, it is highlighted that in all age groups the predominant lesions were in the oropharynx (50%), although those of laryngeal location occurred in 42.5% of patients. As for the location, the absence of lesions in the nostrils in adolescents between 16 and 19 years old is striking.

| Localization | Age groups | | | | | | | | | |
|--------------|----------------------------------|-----|-----------------------------------|------|-----------------------------------|-------|-------------|-----|-------|------|
| | 1- 5 years 11 months and 29 days | | 6 -10 years 11 months and 29 days | | 11-15 years 11 months and 29 days | | 16-19 years | | Total | |
| | No | % | No | % | No | % | No | % | No | % |
| Orophage | 5 | 50 | 4 | 57,1 | 5 | 45,45 | 6 | 50 | 20 | 50 |
| Laryngeal | 4 | 40 | 2 | 28,6 | 5 | 45,45 | 6 | 50 | 17 | 42,5 |
| Nasal | 1 | 10 | 1 | 14,3 | 1 | 9,1 | 0 | 0 | 3 | 7,5 |
| Total | 10 | 100 | 7 | 100 | 11 | 100 | 12 | 100 | 40 | 100 |

Table 2: Distribution of patients according to anatomical location of the lesions and their relationship with the age ranges.

$P \geq 0,05$.

When relating the type of delivery with the maternal history of vaginal infection (Table 3), a statistical association was found between these variables ($p < 0.05$). Transvaginal birth

was associated with the highest number of cases of recurrent respiratory papillomatosis with 34 for 85%.

| Type of delivery | Maternal history | | | | | | |
|----------------------|----------------------------|------|----------------------------|------|-------|-----|-----|
| | Positive vaginal infection | | Negative vaginal infection | | Total | | RR |
| | No | % | No | % | No | % | - |
| Transvaginal | 11 | 78,6 | 23 | 88,5 | 34 | 85 | 4,6 |
| By caesarean section | 3 | 21,4 | 3 | 11,5 | 6 | 15 | 1,9 |
| Total | 14 | 100 | 26 | 100 | 40 | 100 | - |

Table 3: Type of delivery in relation to maternal history of vaginal infection.

Table 4 shows the evolution of patients according to the treatment received, highlighting the monotherapy with acyclovir and the therapeutic combination of excision plus interferon, both

were related to the largest number of patients who had satisfactory evolution (100 and 95.8%) respectively.

| Treatment received | Evolution | | | | | |
|----------------------|--------------|------|------------------|-----|-------|-----|
| | Satisfactory | | Not satisfactory | | Total | |
| | No | % | No | % | No | % |
| Excision /Interferon | 23 | 95,8 | 1 | 4,2 | 24 | 60 |
| Excision/ Acyclovir | 8 | 80 | 2 | 20 | 10 | 25 |
| Exeresis | 1 | 25 | 3 | 75 | 4 | 10 |
| Acyclovir | 2 | 100 | 0 | 0 | 2 | 5 |
| Total | 34 | 85 | 6 | 15 | 40 | 100 |

Table 4: Evolution of patients according to treatment regimen received.

P ≥ 0,05.

Discussion

Recurrent respiratory papillomatosis is a rare disease, its prevalence is 4.3 cases per 100,000 children; according to the United States surveillance centers, this translates into 2000 to 2500 new cases in pediatric population annually [3-5].

The patients who were the subject of analysis represented only 3.17% of the total admissions to the Otolaryngology Service in 7 years of study, which coincides with the reports in the literature regarding the indication of recurrent respiratory papillomatosis as a rare entity in pediatric age.

The human papillomavirus is epitheliotropic with great affinity for tubular organs in contact with the outside such as nostrils, oral cavity, pharynx, larynx, trachea, bronchi, esophagus and vagina [6].

The prr clinic depends largely on its location, the most frequent being those of oropharyngeal and laryngeal location [5-7].

Of the pathologies produced by HPV, oral papilloma is the most frequent epithelial lesion, it has no predilection for sex. It is considered a premalignant lesion and precursor of oral cancer [8-10].

Limongi L and collaborators [11] indicate in the patients studied by them a higher incidence of oral papilloma in the ages between five and eleven years with predominance in the female sex.

When analyzing the distribution of patients according to anatomical location in the present study; it was found that oropharyngeal lesions were the most frequent representing 50%, this coincides with the literature consulted. As for sex, male (60%) predominated, which is not related to other reports.

Juvenile laryngeal papillomatosis is the most common benign laryngeal neoplasm detected at birth and the first years of life Its highest incidence in the first two decades of life places it as the most frequent benign laryngeal tumor lesion of childhood [12].

Laryngeal papillomatosis is an unusual disease compared to the cutaneous and anogenital presentation of HPV infections in infants and when it occurs early in life, it is mainly related to transplacental or perinatal congenital transmission [13].

Bello by Alford M and collaborators [6]. In their study of patients with this entity they found a slight predominance of the female sex with 8/7 females, These results are not consistent with the patients of the present research where the male sex predominated (58.8%).

Castillo Karina H and collaborators [12]. It is noteworthy among the results of the series analyzed by them that there were 120 cases of juvenile laryngeal papillomatosis among 14 400 patients, for a frequency of 0.8%, predominantly the male sex (61.1%). This is similar to those of this casuistry where the same gender predominated (58.8%).

In most cases recurrent respiratory papillomatosis is diagnosed in children between two and four years of age, some observations suggest as risk factors being the child of a primigestant mother, young and of low socioeconomic stratum [5].

Oral papillomatosis affects children and adults, but has a certain predilection for people aged 30 to 50 [8-10].

In this sample there was a slight predominance of oral lesions in adolescents unlike the results of Limongi L and collaborators [11].

In patients with juvenile laryngeal papillomatosis; Bello by Alford M and collaborators [6]. Observed a higher incidence in age groups aged 0 to 10 years.

On the other hand in the studio of Castillo Karina H and collaborators [12]. The average age of patients with this entity was 9 ± 4 years, results similar to those shown in the patients studying in terms of the average age that was 8.6 ± 4 years.

In the patients studied, no statistical association was found between the anatomical location of the lesions caused by HPV and age, however it stands out that in all age groups the predominant lesions were in the oropharynx (50%), the absence of lesions in the nostrils in adolescents between 16 and 19 years is striking.

In the case of laryngeal papillomatosis most authors agree that one of the main forms of contagion is through the ingestion of viral particles or infected cells during the passage of the child through the birth canal in mothers with genital condylomatosis [8,12].

With some frequency they are diagnosed by the clinic and corroborated by biopsies, premalignant lesions in extragenital locations, skin, mouth, conjunctiva, head, neck and larynx in association with HPV and epidemiological and immunological studies confirm their presence [14].

Condyloma acuminata is a common and highly infectious STI, which can be transmitted to the sexual partner and given by the mother to the child, and cause in the latter, juvenile laryngeal papillomatosis [1].

Intrapartum infection rates are lower for those newborns delivered by caesarean section, although there are no strong data to recommend this type of prophylactic delivery [2].

Castillo Karina H [12] also concludes that laryngeal papilloma is most often associated with vaginal birth and genital infection with human papillomavirus during pregnancy.

Izaguirre [13] Describing the epidemiological characteristics of children born to mothers with HPV during pregnancy, it concluded that most of them were full-term products and 75% were born vaginally.

In the present study, a statistical association was found between the type of delivery and maternal histories of vaginal infection, with a value of $p < 0.05$ and an RR (Relative risk) of 4.6. Transvaginal delivery was associated with the highest number of cases of recurrent respiratory papillomatosis (85%) and the history of vaginal infection in pregnancy was also incident in children who developed the entity (78.6%), results these concordant with other reports.

In the usual treatment of recurrent respiratory papillomatosis, multiple surgical procedures are required, due to its recurrent nature, in which the lesions are resected by means of laryngeal microsurgery instruments, laryngeal microdebrider or vaporization of the lesions with CO₂ laser [5].

Children under three years of age have a 3.6 times higher risk of requiring a greater number of annual surgical procedures and of having involvement in more than one anatomical site. The lack of an effective treatment for children with aggressive course of this pathology has led to tests with multiple adjuvant treatment options such as interferon alfa, photodynamic therapy and indole-3-carbinol and more recently with cidofovir [5].

In Cuba, all available therapies are applied systematically, both medical and surgical treatment or both, Barrera Rivera D and collaborators [15]. Report the successful treatment of a patient by applying human interferon and immunomodulators such as biomodulin, immunoglobulin G and transfer factor.

In the patients of the present series, medical, surgical and both combined therapies were applied, 100% of those who received acyclovir as monotherapy had a favorable evolution, however it has no statistical significance since it was only applied in 10% of the patients. Regarding the treatment with excision plus interferon, it was used in 60% of the sample with a favorable evolution of 95.8%.

The above results coincide with the literature consulted in terms of pointing to previous therapies as part of the therapeutic resources currently available, although none of these is fully effective and capable of avoiding relapses in all patients.

Conclusion

It is concluded that the clinical characteristics and epidemiologies of patients with recurrent respiratory papillomatosis of the present casuistry do not differ from the global epidemiological context, being a rare observation entity, but not rare in pediatric services.

Conflict of Interest

The authors declare that they have no conflict of interest.

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