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CLINICAL CASE

Recurrent respiratory papillomatosis in a pediatric patient: case report

Papilomatosis respiratoria recurrente en paciente pediátrico, reporte de un caso

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Abstract

Introduction: Genetic variability related to the host immune system has been proposed as one of the most influential factors in the development of diseases caused by HPV. **Clinical case:** We report the case of a 5-year-old child in whom chronic laryngeal papillomatosis, probably acquired vertically during labor, was detected. The diagnosis of laryngeal papillomatosis was confirmed with a biopsy after a first surgery to remove the papillomas. The Derkay classification system was used to assess the severity of papillomatosis. Biopsy genotyping was performed by demonstrating HPV-6. Later, HLAD-QA1*0505, -DQB1*0301, -DRB1*1101 alleles were homozygous for HLA allele typing. **Conclusions:** Further studies are needed to identify the most prevalent HLA alleles in the Latino population and their potential association with genetic susceptibility in Recurrent Respiratory Papillomatosis.

Keywords:
HLA-alleles;
recurrent respiratory papillomatosis.

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Introduction

The only known disease secondary to perinatal transmission of human papillomavirus (HPV) type 6 or 11 (HPV-6, HPV-11) is recurrent respiratory papillomatosis (RRP)[1]. When symptoms begin to manifest before 5 years old, RRP is generally classified as "juvenile onset" (juvenile-onset; JO-RRP).

The earlier the onsets age of the symptoms, the more severe the disease[2,3]. The incidence of RRP in children varies between 1.7-4.3/100,000, with no significant differences when separated by race or gender[2,4].

There are different risk factors involved in the development of HPV pathology. The genetic variability related to the host immune system has been proposed as one of the most influential, since it could play an important role in the defensive response against the virus[5,6]. Evidence indicates that cellular immunity would be compromised in children with RRP. Patients with a more aggressive clinical course may have an immunodeficiency associated with this immunity[7]. However, it is still unclear whether HPV causes this alteration in immunity or if children with impaired immunity develop RRP. As well as the susceptibility to cervical cancer caused by HPV has been related to some specific HLA alleles, similarly it has been seen that this association is fulfilled in patients with RRP, where certain alleles influence the course of the disease, favoring the severity[8-10] or, on the contrary, fulfilling a protective role[11,12].

Clinical case

A 5-year-old male with prolonged dysphonia (since he was 8 months of age, according to his mother) and a clinical diagnosis of laryngeal papillomatosis. He was admitted to the Otorhinolaryngology Service (ORLS) of the Dr. Hernán Henríquez Aravena Hospital in Temuco, Chile. A gynecological check during pregnancy of the child's mother described vaginal condylomas. However, such lesions were not considered contraindications to vaginal delivery. Although the mother did not receive treatment, the condylomas were not described during labor. Once the patient was admitted to the ORLS, a direct laryngoscopy showed papillomatous lesions in the vocal cords, confirming the diagnosis of laryngeal papillomatosis with a biopsy after a first surgery to remove the papillomas. The Derkay Score system was used to evaluate the severity of papillomatosis[13], which indicated a score of 21, which coincided with a moderate clinical picture. Because papillomatous lesions and dysphonia were recurrent, the child underwent five surgical interventions in total, all of them for therapeutic purposes and always obtaining a sample for biopsy. No adjuvant therapy was considered. The strategy consisted on operating a vocal cord first and three or four months later the contralateral vocal cord, in order to avoid synechia between two bloody surfaces.

Surgeries were performed when the patient was 5 years old and 8 months; 7 years and 2 months; 7 years and 5 months; 8 years and 7 months, and finally 8 years and 11 months of age.

After the second surgery, genotyping was requested for HPV. Using a commercial kit (HPV type 3.5 LCD-Array Kit, Chipron GmbH, Berlin, Germany) and following the manufacturer's instructions, HPV-6 was detected in the patient's laryngeal tissue sample (figure 1).

Immunological exams indicated that levels of cellular immunity markers were normal (BD FacScan, San Jose, CA, USA). Only a slight elevation in serum IgM was found. The level of the other immunoglobulins and complement components were not altered (BN ProSpec System, Siemens, Health Care Diagnostics, Inc.). Primary immunodeficiency or HIV, HCV or HBV infection (Architect i8200, Abbott, Abbott Park, IL, USA) were ruled out (table 1).

For the typing of HLA alleles of the patient, commercial kits were used according to the manufacturer's instructions (Micro SSPTM Allele Specific HLA Class II DNA Typing Tray) (HLA Celiac, Inc. 21001 Kittridge Street, Canoga Park, CA) Disease [PROTRANS medizinische diagnostische Produkte GmbH, Hockenheim, Germany]). The results are summarized in table 2.

Currently, the patient is 11 years and 9 months old, is healthy and has a very good quality of life, he normally attends classes and he is being clinically controlled regularly.

Discussion

To date, no results of a HLA class II allele typing have been published in Chilean children with RRP. However, studies in other populations, mainly Caucasian, describe associations between HLA alleles and susceptibility to RRP.

The HLA analysis in our patient shows a homozygous state for alleles DQA1*0505, DQB1 *0301 and DRB1*1101. The haplotypes DRB1*1101 and DRB1*1101 DQB1*0301 have been strongly associated with susceptibility to severe RRP in Korean patients[14], although a study with patients with JO-RRP and RRP "adult-onset; AO-RRP), mainly Caucasians and to a lesser percentage of African-Americans and Hispanics, revealed that there would be no increase in the prevalence of DQB1*0301 or association of the allele with the severity of the disease[15], which would agree more with our patient showing a moderate cli-

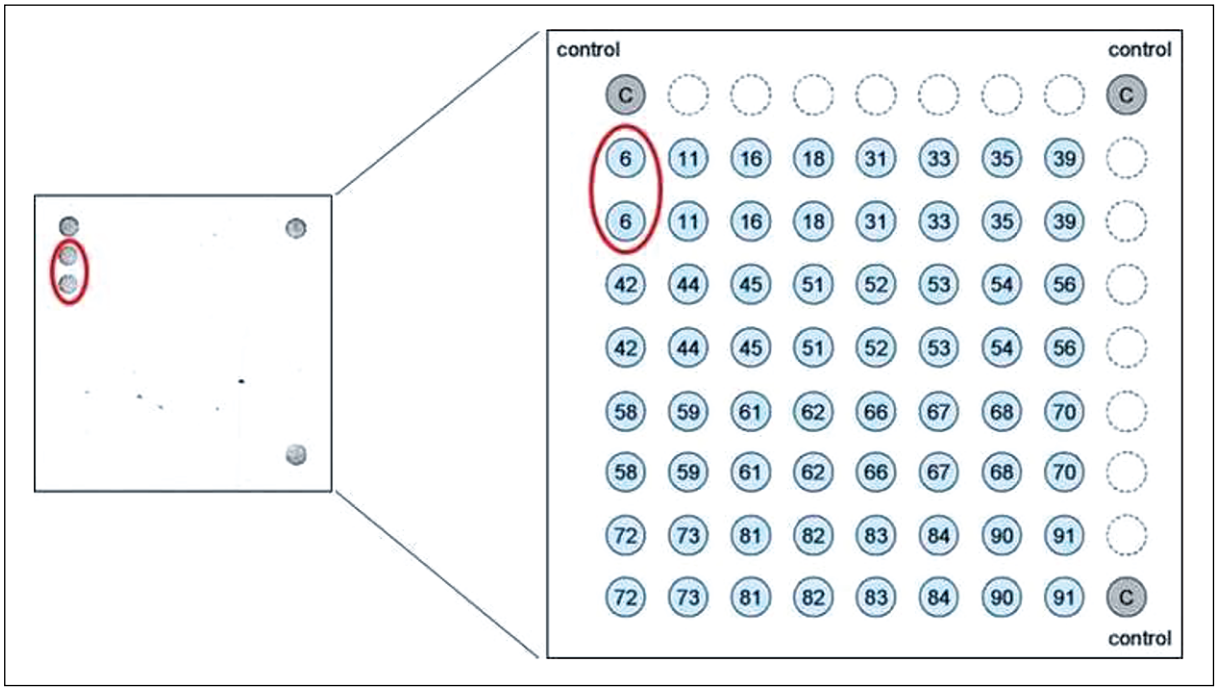

Figure 1. Results of hybridisation with DNA from the patient's laryngeal tissue and specific probes for 32 HPV serotypes on a commercial matrix (*HPV type 3.5 LCD-Array Kit*). Positive result for HPV-6.

Table 1. Cell immunity and serological markers

Test	Results	Range	Method
Total leukocytes	8780 x mm³	5.000 - 15000 x mm³	-
CD19 (B cells)	323 x mm³	200 - 600 x mm³	
CD3 (T cells)	1956 x mm³	700 - 3500 x mm³	Flow Cytometry
CD4 (helper T cells)	935 x mm³	300 - 2100 x mm³	
CD8 (cytotoxic T cells)	925 x mm³	300 - 1200 x mm³	
CD4/CD8 ratio	1.01	0.90 - 3.40	-
CD16+56	401 x mm³	90 - 1200 x mm³	Flow Cytometry
C3	122 mg/dL	80 - 170 mg/dL	
C4	19 mg/dL	14 - 44 mg/dL	
IgG	1334 mg/dL	540 - 1822 mg/dL	Nephelometry
IgA	211 mg/dL	21 - 291 mg/dL	
IgM	221 mg/dL	41 - 183 mg/dL	
Total IgE	70 UI/mL	< 90 UI/mL	
Surface antigen of the Hepatitis B virus (HBsAg)	0.16	< 2.0 (Negative) ≥ 2.0 (Positive)	
Hepatitis C virus (anti-HCV)	0.12	< 1.0 (Non-reactive) ≥ 1.0 (Reactive)	Chemiluminescence
HIV Ag p24, anti-HIV	Negative	-	

Table 2. Typing of HLA class II alleles

HLA allele	Absent	Heterozygote	Homozygote
DQA1*0505	-	-	X
DQB1*0301	-	-	X
DRB1*1101	-	-	X

nical picture, and a Derkay score of 21. Up to now the DQA1*0505 allele has not been associated with RRP susceptibility or HPV infection, however, interestingly, the DRB1*11-DQA1*0505 alleles have been associated with Variable immunodeficiency in Iranian patients[16]. However, in our case, a known primary im-

munodeficiency and an immunodeficiency secondary to HIV were ruled out.

To date, published information concerning HLA genes and their possible association with RRP susceptibility refers primarily to alleles other than those published in this case. HLA-DRB1*14 has been associated with susceptibility to JO-RRP, whereas HLA-DRB1*0301 with susceptibility to AO-RRP. Interestingly, patients homozygous for HLA-DRB1*0301 show a more severe clinical picture[8].

Also, it has been shown that the HLA-DQA and HLA-DQB1 alleles present in different proportions in children with RRP regarding their controls. In addition to influencing the risk of RRP, the frequencies of alleles and haplotypes mentioned have some influence on the course of the disease, regardless of the HPV genotype involved[10].

In 2004 it was suggested for the first time that a high frequency of HLA- DRB1*0102 was associated with predisposition to RRP in Caucasian individuals. The HLA-DRB1*0301, DQB1*0201 and DQB1*0202 alleles showed increased frequency in Caucasians with severe disease, indicating that such alleles could be involved in regulating the severity of the disease. Interestingly, HLA-DRB1*0301 and DQB1*0201 were associated with reduced interferon-gamma (IFN-γ) expression. On the other hand, the HLA-DQB1*0602 allele was more frequent in controls than in Caucasians with severe disease, suggesting a control effect of the severity by that allele. While DQB1*0602 was absent, the DQB1*0201 and DQB1*0202 alleles showed increased frequency in African Americans[9]. More recently, only results indicating a potential protective role for DQB1*0602 could be replicated by Rodier C. et al. (eleven). Similarly, another study shows that about 80% of patients with severe RRP lack this protective allele[12]. An important ethnic difference has to do with the HLA-DQA*0102 allele, whose presence is associated with a high risk of developing RRP in Caucasian patients but with remission of the disease in African American patients[10].

From the HLA typing of our patient it is inferred that the HLA-DQA*0102, DQB1*0201, DQB1*0202, DQB1*0602, DRB1*0102, DRB1*0301 and DRB1*14 alleles are not present.

To date, studies reported on HLA genes and susceptibility to RRP mainly involve work with Caucasian patients, with some ethnic variability in the results. We believe that future studies in Latin populations are necessary to determine the prevalence of HLA alleles, their potential association with genetic susceptibility to RRP, the severity of the clinical picture and the influence on the course of the disease in these patients. Similarly, it is important to determine a link between these alleles and some known or unknown primary immunodeficiency, which could be a prior history that facilitates HPV infection or a consequence thereof.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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