Treatment of human papillomavirus in childhood with imiquimod 5% cream

Tratamento do papiloma vírus humano na infância com creme de imiquimode a 5%

Hebert Roberto Clivati Brandt [1]
Regia Celli Ribeiro Patriota [3]
Walter Belda Junior [5]
Juliana Dumêt Fernandes [2]
Paulo Ricardo Criado [4]

Abstract: In children, lesions caused by the human papillomavirus (HPV) constitute a significant epidemiological issue and a therapeutic dilemma, particularly in the case of anogenital warts. The treatment of anogenital warts in children is a challenge, since standard treatments are generally painful and require the patient to be anesthetized. Imiquimod, a topical immune response modifier, constitutes an alternative therapeutic agent for the treatment of HPV. The present report describes four cases in which treatment with topically applied imiquimod 5% cream was implemented with successful results.
Keywords: Aminoquinolines; Human papillomavirus 6; Human papillomavirus 11; Interferon inducers; Papillomavirus infections

Resumo: Lesões decorrentes da infecção pelo papilomavírus humano na infância, em especial as verrugas anogenitais, são um importante problema epidemiológico e terapêutico. O tratamento das verrugas anogenitais na infância é um desafio terapêutico. Os tratamentos convencionais geralmente são dolorosos e necessitam de anestesia geral. O imiquimode, um imunomodulador tópico, constitui uma alternativa terapêutica. Serão descritos quatro casos tratados com sucesso utilizando creme de imiquimode a 5% aplicado topicamente.
Palavras-chave: Aminoquinolinas; Indutores de interferon; Infecções por papillomavirus; Papillomavirus 6 humano; Papillomavirus 11 humano

Received on 02.07.2009.
Approved by the Advisory Board and accepted for publication on 31.07.2009.
* Study conducted at the Outpatient Clinic of Sexually Transmitted Diseases, Department of Clinical Dermatology, Teaching Hospital, FAMUSP, São Paulo, SP, Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

[1] Preceptor, Dermatology Department of the Teaching Hospital, School of Medicine, University of São Paulo (FMUSP), São Paulo, SP, Brazil.
[2] Currently participating in a doctoral program at the Department of Dermatology, School of Medicine, University of São Paulo (FMUSP). Collaborating physician at the Department of Dermatology, School of Medicine, University of São Paulo (FMUSP), São Paulo, SP, Brazil.
[3] Masters degree in Dermatology from the Department of Dermatology, School of Medicine, University of São Paulo (FMUSP). Physician, Department of Dermatology of the Teaching Hospital, School of Medicine, University of São Paulo (FMUSP), São Paulo, SP, Brazil.
[4] Doctorate degree in Medicine from the Department of Dermatology, School of Medicine, University of São Paulo (FMUSP). Assistant physician, Department of Clinical Dermatology and investigator at the Medical Research Laboratory, LIM 53, of the Teaching Hospital, School of Medicine, University of São Paulo (FMUSP), São Paulo, SP, Brazil.
[5] Doctorate degree in Medicine from the Department of Dermatology, School of Medicine, University of São Paulo (FMUSP). Faculty, Dermatology Department, University of Campinas (UNICAMP). Head of the Division of Sexually Transmitted Diseases/AIDS of the Brazilian Society of Dermatology. Professor of the Department of Dermatology, School of Medicine, University of São Paulo (FMUSP), São Paulo, SP, Brazil.

INTRODUCTION

Lesions resulting from the human papillomavirus infection, particularly genital warts, in childhood constitute a significant epidemiological issue and a therapeutic dilemma. [1] The principal sites affected by the human papillomavirus (HPV) in children are the extremities and the face, anogenital warts being less common in childhood. [2] The mode of HPV transmission remains controversial, but includes perinatal transmission, auto- and hetero-inoculation, sexual abuse and possibly indirect transmission via fomites. [3] Anogenital lesions detected during a child's first year of life are generally acquired perinatally. Nevertheless, doubts persist with respect to the origin of new lesions that appear between the first and third years of life. [4]

Treatment of extensive condylomatous lesions in childhood represents a therapeutic problem. Ablative procedures and laser surgery are painful and usually require general anesthesia. Topical imiquimod 5% cream has been successfully used for the treatment of condyloma acuminata in adults; however, its use in children has yet to be established. [5]

CASE REPORTS

Case 1

A two-year old boy. His mother reported disseminated perianal lesions over the previous 12 months, increasing in number and size. Multiple confluent brownish papules were observed, affecting the scrotum and perineal and inguinal regions (Figure 1). Previous treatment with 70% trichloroacetic acid was unsuccessful. The child had been born at term following an uncomplicated vaginal delivery. His mother reported having had genital warts during pregnancy. The father was evaluated and no evidence was found of any genital lesions or extragenital warts.

Case 2

A one-year old male patient. His mother reported multiple perianal lesions of six months' duration. Skin-colored papules were found in the perianal region (Figure 2). Previous treatment with 25% podophyllin was unsuccessful. The child was born at term following an uncomplicated vaginal delivery. His parents had no HPV-associated lesions.

Case 3

A two-year old girl. Her mother reported genital lesions of four months' duration. Multiple skin-colored papules were found in the vulvar and perianal region. The child was born at term following an uncomplicated vaginal delivery. Gynecological examination revealed signs of a ruptured hymen and other evidence of vaginal trauma. Following meticulous evaluation, signs of sexual abuse were detected.

Case 4

An 18-month old girl. Her mother reported genital lesions of six months' duration. Multiple skin-colored papules were found in the perianal region. The child was born at term following an uncomplicated vaginal delivery. Gynecological examination showed no abnormalities. Past history of sexual abuse.

A virological study of the lesions in the first three patients using polymerase chain reaction (PCR) resulted in positivity for HPV-6 and HPV-11 in all three cases. PCR was not performed in case 4. In all four cases, histopathology was compatible with condyloma. Other findings included papillomatosis and acanthosis, thickening and lengthening of the skin ridges, associated with koilocytosis. Serology for syphilis, hepatitis B and C and HIV was negative in all four cases.

The four cases were treated topically with

Figure 1: Case 1. Multiple brownish, confluent papules affecting the scrotum, perianal and inguinal regions, prior to treatment

Figure 2: Case 2. Multiple papules converging in skin-colored plaques in the perianal region, prior to treatment

imiquimod 5% cream applied at home three times a week. Complete regression of the lesions occurred after three weeks of use in cases 1 (Figure 3) and 3, and after four weeks in cases 2 and 4 (Figure 4). Treatment was continued for a total of six weeks in all cases. Only one adverse event was recorded, consisting of moderate erythema on the perilesional skin identified in case 1; however, the condition improved as treatment progressed. After six months of follow-up, no new clinical lesions were found in any of the four cases.

DISCUSSION

In adults, the transmission of genital warts occurs mainly by sexual contact. Genital warts in childhood may be acquired through nonsexual contact. Condyloma acuminatum has been described in 1-2% of cases of child sexual abuse, and 50-75% of the cases of genital warts in children are a consequence of sexual abuse. [6] HPV subtypes 6 and 11 have been associated with child sexual abuse more frequently than subtypes 2 and 3. [7] Perinatal transmission of genital warts from infected mothers to the external genitalia of their infants has been well-documented. [8] HPV transmission through close contact with their carers has also been reported. Due to the possibility that children with external genital warts may have been sexually abused, communication with the relevant child protection agency is indicated if there is a strong suspicion of abuse based on the patient's history and physical examination. [9]

Treatment of lesions resulting from HPV should be individualized. Various sessions with different therapeutic modalities may be required to achieve complete regression of the lesions. The conventional treatment consists of chemical destruction of the lesion by topical application of podophyllin, 5-fluorouracil, bi- or trichloroacetic acid and podophyllotoxin. Methods of physical destruction of lesions include cryotherapy, laser, electrocauterization and surgical excision. [10] Physical methods are often painful, may result in scarring and require the use of anesthesia. Recurrence of the lesions is common. These repeated and painful applications on the genitalia of a child may lead to psychological disturbances. [10,11]

Treatments based on the chemical or physical destruction of the infected keratinocytes do not directly inhibit the infection or viral replication. Each therapeutic option has its own inherent advantages and disadvantages, and there is no medication up to the present time that effectively eliminates HPV. [12]

The innate immune system, which defends the host against viruses, is composed of natural killer cells and activated macrophages. Viral infection of the lymphocytes results in the production of antiviral cytokines, the interferons, which activate various mechanisms that act against the virus in cells that are not yet infected, rendering them resistant to infection. Specific adaptive immune responses are then activated, principally by cytotoxic T-cells, auxiliary T cells and antibodies that neutralize the virus, preventing reinfection and dissemination in extracellular phases. The complement also exerts activity on viral infections. Toll-like receptors (TLR), which are involved in recognizing the viral pathogen-associated molecular patterns (PAMPs) such as TLR 2-4, 7-9, are also involved in this process. [2, 12]

The persistence of HPV-induced lesions is principally a consequence of defective immunosurveillance. [1] Modulation of the immune response by systemic, topical or intralesional medication represents an alternative treatment for viral infections. The efficacy of this modulation is based on the regression of

Figure 3: Case 1. Total regression of the lesions after three weeks of imiquimod treatment

Figure 4: Case 2. Total regression of the lesions after four weeks of imiquimod treatment

verrucous lesions resulting from the development of specific immunity to HPV.

Imiquimod is a synthetic immunomodulator for topical use. It is an aminoquinoline compound and exerts an effect on the cellular innate immune system mediated by interferon alpha and tumor necrosis factor-alpha. There is also an increase in innate and acquired immunity through stimulation of the toll-like receptors of the antigen-presenting cells. Activation of the immune mediators appears to be responsible for eradicating the HPV virus. Imiquimod induces the production of interferon-alpha (IFN-a) by the keratinocytes, as well as other cytokines that inhibit viral replication. Imiquimod also acts on cell immunity by activating Langerhans cells, thus increasing the presentation of antigens for the T-cells. [1,11,13]

Imiquimod treatment of lesions resulting from a viral infection such as condyloma acuminatum in adults and viral warts and mollusca contagiosa in children has shown good results. [13] Complete regression of the lesions is achieved in 72-84% of cases, local recurrence rates ranging from 5 to 19%. The advantage of this treatment for children is the convenience of a treatment that can be applied painlessly in the home, which is not the case with many of the ablative therapies. [11,12] Imiquimod 5% cream is well tolerated, the most common adverse events being erythema, burning, erosion and hypersensitivity, which are usually limited to the site of application. Systemic absorption of imiquimod is less than 1% of the total amount applied topically and is more associated with the surface area than with the quantity applied. Systemic symptoms are rare; however, patients may present fatigue, fever, myalgia, alterations to the central and peripheral nervous system and gastrointestinal symptoms. [13]

Lesions located in the mucosa are more responsive to treatment, possibly due to better absorption. [13] The efficacy of treatment may be greater if imiquimod is used more frequently or in combination with topical salicylic acid or retinoic acid. In refractory cases, imiquimod may be applied under an occlusive dressing. [13]

The application of imiquimod has proven beneficial for the treatment of condyloma in adults. Nevertheless, its use in children is yet to be established. The principal advantage for children is the convenience of home treatment and the absence of pain. The number of cases in which local irritation led to discontinuation of treatment is minimal, and careful application, avoiding contact with normal skin or decreasing the frequency of use, minimizes this risk.

Complete regression of condyloma was reported in children of 6 and 19 months following application of imiquimod for 3 and 8 weeks, respectively. [11,15] Despite the frequent observation of perilesional erythema, no significant side effects were found in the cases reported or in the cases presented here.

The observation of these four successfully treated cases of genital warts in childhood suggests that imiquimod 5% cream is a safe, effective alternative therapy that should be considered as an option to aggressive painful treatments and also to surgical treatment. ❑

REFERENCES

1. Tchernev G. Sexually transmitted papillomavirus infections: epidemiology, pathogenesis, clinic, morphology, important differential diagnostic aspects, current diagnostic and treatment options. An Bras Dermatol. 2009;84:377-89.
2. Grussendorf-Conen EI, Jacobs S. Efficacy of imiquimod 5% cream in the treatment of recalcitrant warts in children. Pediatr Dermatol. 2002;19:263-6.
3. Syrjanen S, Puranen M. Human papillomavirus infections in children: the potential role of maternal transmission. Crit Rev Oral Biol Med. 2000;11:259 -74.
4. Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. Obstet Gynecol. 1998;91:92-6.
5. Belda Jr. W, Shiratsu R, Pinto V. Abordagem nas doenças sexualmente transmissíveis. An Bras Dermatol. 2009;84:151-9.
6. Shwarcz SK, Whittington WL. Sexual assault and sexually transmitted diseases: detection and management in adults and children. Rev Infect Dis. 1990;12:S682-9.
7. Gutman LT, Herman-Giddens ME, Phelps WC. Transmission of human genital papilloma virus disease: comparison of data from adults to children. Pediatrics. 1993;91:31-8.
8. Pakarian F, Kaye J, Cason J, Kell B, Jewers R, Derias NW, et al. Cancer associated human papilomavirus: perinatal transmission and persistence. Br J Obstet Gynecol. 1994;101:514-7.
9. Gutman LT, St Claire K, Herman-Giddens ME, Johnston WW, Phelps WC. Evaluation of sexually abused and nonabused young girls for intravaginal human papillomavirus infection. Am J Dis Child. 1992;146:694-9.
10. Moresi JM, Herbert CR, Cohen BA. Treatment of anogenital warts in children with topical 0. 05% podofilox gel and 5% imiquimod cream. Pediatr Dermatol. 2001;18:448-50.
11. Schaen L, Mercurio MG. Treatment of human papilloma virus in a 6-month-old infant with imiquimod 5% cream. Pediatr Dermatol. 2001;18:450-2.
12. Chang GJ, Welton ML. Human papillomavirus, condylomata acuminata e anal neoplasia. Clin Colon Rectal Surg. 2004;17:221-30.
13. Chang YC, Madkan V, Cook-Norris R, Sra K, Tyring S. Current and potential uses of imiquimod. South Med J. 2005;98:914 -20.
14. Gruber PC, Wilkinson J. Successful treatment of perianal warts in a child with 5% imiquimod cream. J Dermatol Treat. 2001;12:215-7.
15. Malewski S, Pniewski T, Malejczyk M, Jablonska S. Imiquimod is highly effective for extensive, hyperproliferative condyloma in children. Pediatric Dermatol. 2003;20:440-2.

MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:
Hebert Roberto Clivati Brandt
Av. Dr. Enéas Carvalho de Aguiar, 255 - 3º andar
Divisão de Clínica Dermatológica - ICHC
05403 000 São Paulo - SP, Brazil
Tel.fax: +55 11 3069 8002; +55 11 3088 9145
E-mail: hebertbrandt@yahoo.com.br

How to cite this article/*Como citar este artigo*: Brandt HRC, Fernandes JD, Patriota RCR, Criado PR, Belda W Jr. Treatment of human papillomavirus in childhood with imiquimod 5% cream. An Bras Dermatol. 2010;85(4):549-53.