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Paediatric Anogenital Condylomata Acuminata: An assessment of patient characteristics and the need for surgical intervention

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ABSTRACT

Background: Anogenital Condylomata Acuminata (AGCA) are caused by Human Papilloma Virus (HPV), which is one of the most common sexually transmitted illnesses in adults. Although commonly seen in the paediatric population, especially in the setting of immunocompromise, literature regarding transmission, viral type and management in this population is scant. The aim of this study was to assess the profile of patients presenting with anogenital warts in light of associated immunocompromise with Human Immunodeficiency Virus (HIV).

Methods: Three years of patient records from Chis Hani Baragwanath Academic Hospital were reviewed (January 2017 – December 2019). Information collected included: gender, age of presentation, age at intervention, type and duration of medical treatment, type and number of surgical interventions, HIV status, and histology results. Fisher's and Pearson's test were used to assess correlation between immune status and surgical interventions necessary.

Results: In the time frame considered, we treated 66 patients with AGCA . The average age was 4 years old (1–14). HIV status was recorded in 30 patients (15 positive and 15 negative). Only one patient out of 66 had a history of sexual abuse. Whilst the proportion of patients who required surgical intervention in the HIV negative and HIV positive groups was equal (2:1), the total number of surgical interventions needed to achieve clearance was significantly more in those with HIV ($p = 0.03$).

Conclusions: HIV positive patients with AGCA require more surgical interventions compared to HIV negative individuals. Further research will be conducted to ascertain the sub-type of HPV infection in this subset of patients and to assess if this impacts follow-up for future malignancy. Further research also needs to be conducted to ascertain whether surgical intervention should be instituted earlier in the treatment protocol for HIV positive children.

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1. Introduction

Anogenital Condylomata Acuminata (AGCA) (also known as anogenital warts) are caused by the Human Papilloma Virus (HPV). Over 100 strains of HPV exist and can manifest as warts in various areas of the body, including the hands, feet, genitals and the peri–anal area. Eighty percent of adults are thought to be infected with HPV and it is the most common sexually transmitted disease (STD) worldwide, with 10% of adults presenting with AGCA [1]. The strains that most often cause AGCA are 6 and 11, whilst HPV 1, 4, 16 and 18 are less prevalent causes [2]. The virus can manifest as benign or malignant lesions on many areas of the body, including the genitals. There are two strains of HPV that have been shown to be high-risk oncogenic subtypes (HPV 16 and 18), causing dysplasia of cells in the affected area. Other strains of HPV have a low oncogenic risk but they can cause pain, pruritus, and bleeding [2]. Types 6 and 11 are the strains that are isolated from AGCA in adults in 75%–90% of cases [1].

In children, routes of transmission can be separated into vertical transmission from perinatal infection (in up to 25% of the paediatric population and more commonly in children whose mother's report genital warts or cervical dysplasia perinatally [3,4]) or horizontal inoculation (either autoinoculation from warts on the child's own fingers or hetero-inoculation from warts on a sibling or caregiver's hands) [1,2]. Child Sexual Assault (CSA) is a type of horizontal transmission. However, CSA being implicated as the mode of transmission increases with age and very few children under 4 years old acquire AGCA by sexual transmission [2]. Horizontal inoculation usually transmits warts containing cutaneous subtypes of the HPV virus (types 1–5 and 7).

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While 10% to 20% of children will have cutaneous warts at some time during their childhood [1], the number of children that experience AGCAs is much lower. This said, the incidence of AGCA in children mirrors that of adults in that it has increased over the past decades [2,5]. This may merely be due to increased testing and awareness, or due to increasing prevalence in the adult population, leading to more children being infected with HPV [3]. The incubation period from time of infection to presentation with AGCA can range from weeks to months, making identifying the route of transmission difficult [4]. The age of onset of AGCA was reported to be below 2 years old in 28% of children, and between 2 and 6 years old in 62%, with the mean age of onset being 3 years and 9 months old [3].

The burden of Human Immunodeficiency Virus (HIV) cannot be overlooked in the South African setting. A UNAIDS (United Nations Programme on HIV/AIDS) data report of South Africa (SA) showed that 340 000 children, aged 0–14 years old, were living with HIV in 2019 [6]. The majority of these children are infected vertically but the risk of transmission secondary to CSA cannot be ruled out.

Two thirds of warts should resolve spontaneously within two years, but this is not the case for those who are immunocompromised due to HIV, immunosuppressants or other medical conditions leading to immunodeficiency [2]. Treatment is advised for all unresolving warts or those that have complicated with bleeding, pain, pruritis or infection [3]. There are a variety of medical and surgical treatments available [1,2,4].

In our institution the management of patients with AGCA includes the following:

When children with AGCA are referred to our clinic a thorough history is taken. If previous HIV testing is not available then the test is repeated to exclude HIV. Subsequently all patients are started on medical management with Imiquimod [4]. After 6 weeks patients are reassessed and if no improvement was recorded, surgical intervention is considered. Surgical intervention may include cauterization of the warts (if they are pedunculated with a thin stalk – the wart is cauterized down to the pedicle) or surgical excision, which is utilized in children with large tumour-like wart masses with a broad base of attachment that need to be excised from the skin base. If at the first assessment the warts are deemed so severe to potentially cause bowel obstruction or perineal sepsis then the patient is immediately admitted and an end colostomy is fashioned.

Patients are optimized prior to the surgical intervention to ensure the best possible outcome. This includes monitoring haemoglobin levels, ensuring that patients are not malnourished, and identifying patients who are HIV positive. In patients who are anaemic, a blood transfusion would be administered where necessary. In patients who are found to be HV positive, their CD4 counts are monitored. During the cauterization/excision procedure all members of the team in theatre wear N95 (or equivalent) masks to protect from inhaling smoke from the electrocautery device which may carry viral DNA and lead to HPV infection in operating theatre staff [7]. The patient is placed in lithotomy position and the surgical area undergoes a pre-scrub with chlorhexidine wash. The surgical area is then prepared with a betadine surgical scrub and routine sterile draping. The surgeon sits between the legs of the patient to operate while an assistant stands to the side with a Yankauer suction catheter to remove as much smoke as possible from the operating field in order to prevent inhalation by theatre staff. In patients who have smaller pedunculated or patchy warts – electrocautery of the wart itself is performed until the wart pedicle is cauterized. For those patients with extensive AGCA (Buschke-Lowenstein tumors), we prefer to perform surgical excision (Fig. 2). As such, we perform a shallow surgical excision down to the subdermal layer. In patients who have circumferential warts at the anus we stage the surgical management and only excise 1 or 2 of the peri–anal quadrants at a time so as to prevent strictures and anal stenosis with healing. Once the procedure is complete, the wound is dressed with paraffin gauze and the patient is usually admitted overnight for pain control and initiation of betadine sitz baths.

Although there is very little data on HPV infections in the South African paediatric population, it can be postulated that the prevalence of AGCAs would be higher than that of many other countries where HIV is not endemic. Furthermore, the high prevalence of HIV immunocompromise may infer lower clearance rates with medical and surgical measures and that many children may be affected by progressive and recalcitrant forms of AGCA. With this in mind, the aim of this study was to review our paediatric AGCA population in South Africa with specific relation to surgical management in patients with immunocompromise secondary to HIV infection and to assess if these HPV infections are indeed recalcitrant compared to the immunocompetent population.

2. Material and methods

Ethics clearance for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (M200452). A retrospective cohort study was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH) after reviewing the files for all patients between 0 and 18 years old who presented to the Paediatric Colorectal Clinic for management of AGCA from January 2017 to December 2019 (3-year period). Patients over the age of 18 were excluded. Files for inclusion were identified from the existing electronic database for the Department of Paediatric Surgery Colorectal Clinic. Data collected from online patient records were de-identified, and anonymized data was entered into a study database using Microsoft Excel. Information collected included: Gender, age of presentation, age at intervention, type and duration of medical treatment, type of surgical intervention and number of associated procedures, HIV status, and histology results if histology was requested (as this is not part of our standard operating procedure).

Statistical analysis was performed using Fisher's exact test to test significance of HIV status related to the number of patients requiring surgical intervention and a Pearson's correlation coefficient, which was used to determine correlation between HIV status and the number of surgical interventions required per patient. A p-value less than 0.05 was considered significant.

3. Results

Over the 3-year period, 66 patients with AGCA were attended to at the CHBAH Paediatric Colorectal Clinic. One patient was lost to follow-up and their file could not be located, and was therefore, excluded from this study. Of the 65 remaining patients, 30 were female and 35 were male. The average age of presentation for all patients was 4 years old (Range 1 – 14 years of age) with females presenting, on average, only a few months younger than males (4.1 vs. 4.4 years of age). Only 1 patient in the cohort had a documented history of sexual abuse. Twenty-seven patients (40%) were documented to have received medical treatment. Combination treatment was used by three patients, which included different mixtures of Podophyllin, Benzoin tincture, salicylic acid and silver nitrate. Of these 27, eight patients (30%) went on to have recorded resolution or improvement of warts. One patient had AGCA resolved on combination therapy with podophyllin and salicylic acid. However, these therapies were complicated by severe anal burns necessitating admission to the CHBAH burns unit for further management.

Twenty-three patients necessitated surgical intervention of their AGCA. Five out of 23 patients failed medical management

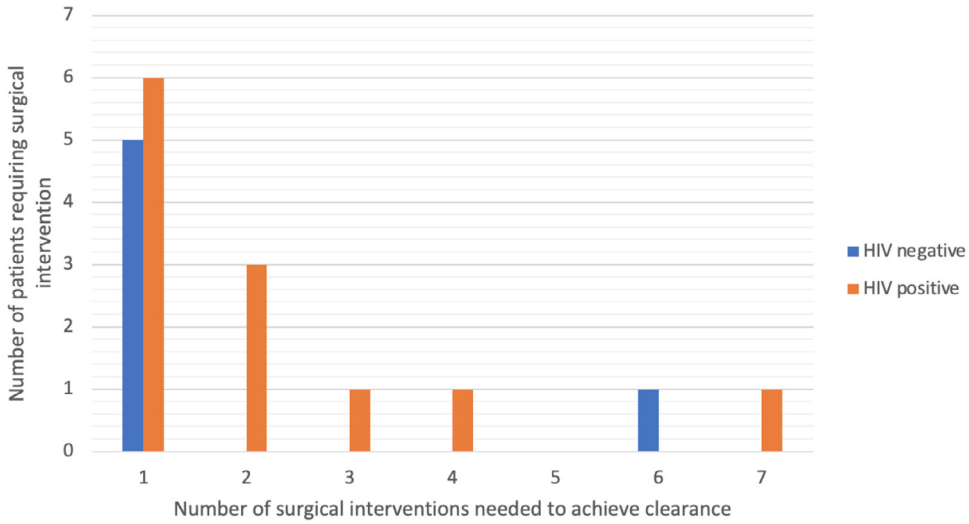


Fig. 1. The number of surgical interventions needed to achieve resolution of AGCA per a patient in the HIV positive and HIV negative groups.



Fig. 2. A patient with a Buschke-Lowenstein tumour seen pre- and post-surgical excision.

prior to surgical intervention, and 18/23 required immediate surgical intervention prior to medical management due to the severity of the AGCA. Ten females required a total of 14 surgical procedures while 13 males required 28 surgical procedures. There was no significant difference in the total number of patients requiring surgical intervention procedures between the genders ($p = 0.396$). Although all patients that present with AGCA are asked about their HIV status, within this cohort, only 30 patients had documented HIV results. Of these patients, 15 were HIV positive and 15 were HIV negative.

Of the 15 recorded HIV positive patients, 80% (12 patients) required a total of 26 surgical procedures to attain resolution of warts whereas, of the HIV negative patients, 40% (6 patients) required 11 surgical procedures to attain resolution. The number of patients requiring surgical intervention in each group was not statistically significant ($p = 0.177$). A Pearson's correlation coefficient was used here to assess the correlation of HIV positivity with number of surgical procedures required per patient to attain clinical resolution of AGCA (Fig. 1). The number of surgical interventions required per patient to attain complete clinical resolution was significantly higher in the HIV positive group compared to the HIV negative group ($p = 0.035$).

As it is not standard practice in our department to send specimens for histology when cauterizing warts, only 11 out of 23 patients' specimens had histological analysis. These specimens were sent at the surgeon's discretion, usually when the surgeon was concerned about possibly malignant or infected warts. No malignancy was noted on any of the specimens. Only 2 of the specimens were evaluated for HPV subtype and these results showed HPV-6 in both specimens. Neither of the specimens evaluated for HPV subtype were from HIV positive patients.

4. Discussion

In our cohort there is a slightly higher incidence of warts of AGCA in males (1:1.2). The almost equal gender distribution is not consistent with global trends where females are 3 times more likely to have AGCA (thought to be due to the higher risk of female children being victims of CSA [2,3], which we were unable to confirm in this review). With only one patient in our cohort having been subject to CSA, this gender equality portends to the transmission in our population being far more likely to be vertical in nature (from the mother during birth) or horizontal due to auto or hetero-inoculation, compared to CSA. At the CHBAH Paediatric Colorectal Clinic, it is standard practice to ask all patients presenting with AGCA about a history of sexual abuse. However, CSA may be under reported as children may be brought to the clinic by parent or caregiver who do not live in the same residence as the child. Females in this cohort presented only slightly younger than the males, with the average age of presentation for the entire cohort at 4 years old, which is consistent with global trends [1,3].

Although 27 patients referred to our clinic had received, or were currently receiving, medical treatment (20 of whom received Imiquimod), only 30% of these patients exhibited resolution or improvement of AGCA which, is a very low percentage considering that two thirds of all AGCAs are reported to resolve spontaneously and that 75% should clear with Imiquimod treatment [1]. Medical agents have been found to be less effective in those with immunocompromise [4]. It is also important to note that 13 patients required immediate surgical intervention of AGCA on referral to our clinic due to the severity of the warts at presentation precluding the use of topical therapy with Imiquimod. There is a paucity of information on the efficacy of surgical intervention in the paediatric population, however, in adults the rate of clearing warts is 57–100% [2].

Of the 30 patients in this cohort that required surgical intervention, 15 (50%) were HIV positive. There is a paucity of data on the prevalence of HIV in the paediatric population but the prevalence of HIV in the adult population (15- to 49-year-olds) is 19.1% [6]. The paediatric prevalence would be expected to be lower than 19.1% as most infections in the paediatric population would likely

be from vertical transmission. Adults who have HIV may have acquired it from vertical or horizontal transmission. This indicates that this cohort of children, presenting for AGCA, had a relatively high prevalence of HIV. This is expected in light of the intimate relationship between immunocompromise and AGCA seen in all populations but especially with HIV co-infection [8]. While gender held no bias in patients requiring surgical intervention, HIV infection certainly did. When one first appraises the data, it appears that patients in both the HIV positive and HIV negative groups required the same proportion of surgical interventions – 12 HIV positive patients receiving 26 surgical interventions (~1:2) and 6 HIV negative patients receiving 11 surgical interventions (~1:2). However, this needs to be considered in the context of the number of patients in each group that required surgery with 80% of the HIV positive patients requiring surgery compared to only 40% of the HIV negative patients. One then needs to consider this HIV status with respect to each patient in the group and how many surgical interventions each patient required in order to macroscopically clear the AGCA. When we looked at this using Pearson's correlation coefficient, the significance is evident with HIV positive patients requiring more surgical interventions than HIV negative patients ($p = 0.035$). This proves the recalcitrant nature of AGCAs seen in the HIV positive population.

Transmission of HPV (causing AGCAs) in children is usually reported to be secondary to horizontal transmission – auto or hetero-inoculation or through CSA. As stated previously, this cohort of patients did not prove CSA to be an important vector for transmission with only one patient reported to have been a victim of CSA. This needs to be interpreted with caution however, based on the knowledge that South Africa has a high rate of sexual abuse [9]. It may be that the history of sexual abuse was either not forthcoming or was unknown by the guardian that brought the patient to the clinic as they may not be the primary caregiver for the child (as is common in the South African context). It is likely that our population is infected vertically, through transmission of HPV during childbirth. Considering the high prevalence of HIV in this cohort, it is likely that HIV is also transmitted to the child during childbirth if the mother is co-infected with both HPV and HIV. With no history of CSA, it is assumed that the HIV positive patients in this cohort were infected with HIV through vertical transmission.

This likely mode of transmission begs answer to interesting questions. If the mode of transmission is vertical, is this paediatric population infected with HPV strains more common in the adult population (e.g. strains 6, 11 and 16)? If so, what are the long-term implications of this infection from an oncological perspective? As the performance of histology and viral subtyping on specimens from our unit has not been standard practice, only 11 specimens were sent of which none had any malignant change. Only 2 specimens had viral subtyping. Both viral subtypes were HPV-6 which is a mucosal strain found in 70–90% of the adult population, but only 34% of the paediatric population [1,3]. To our knowledge, there have been no long-term studies recording the outcome of patients with paediatric AGCA in the setting of HIV.

One of the limitations of this study is the inclusion of patients seen only at our clinic. It should be noted that many patients with AGCA are treated by colleagues in paediatric and dermatology disciplines and therefore, our cohort may be skewed towards patients with more severe AGCA. The retrospective nature of this study also brings with it notable limitations including those of inaccurate record keeping and selection bias. We have designed a prospective study to mitigate these limitations and to study some important parameters. These include whether or not patients receiving surgical intervention are cured histologically of AGCA, if they present with recurring AGCA, or repeated infection. Furthermore, the study assesses whether paediatric patients are infected with oncogenic HPV subtypes (HPV 16 and 18) via vertical transmission and whether they have adult type sequelae including malignancy.

5. Conclusion

This single centre audit suggests a correlation between recalcitrant AGCA needing multiple surgical interventions and children with HIV infection. Patients needing repeated surgical interventions places a massive burden on our already strained health system in a public setting in a low-to-middle-income country. This study infers the need for early surgical intervention in HIV positive patients where AGCA are less likely to resolve spontaneously or respond to medical therapy. This study has forced the authors to attempt to answer questions specific to the type of transmission, viral subtype and long-term outcome in this population group that we hope to attain in a prospective study designed for this purpose.

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Declarations of Competing Interest

None.

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