Journal of Vaccinology

Commentary Article Open Access

Commentary: Human papillomavirus types causing recurrent respiratory papillomatosis in Zimbabwe

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Article Info

Article Notes
Received: April 9, 2019
Accepted: May 30, 2019

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Keywords:
HPV
RRP
Zimbabwe
Vaccination
JoRRP
Genotyping

Abstract

A recent publication describes both the clinical characteristics and human papillomavirus (HPV) types causing recurrent respiratory papillomatosis (RRP) in a Zimbabwean population. Recurrent respiratory papillomatosis is a rare benign disease characterised by recurrent development of exophytic lesions of the connective tissues covering the epithelial cells of the larynx, and in some severe cases the trachea and bronchial tree. Nationwide vaccination against human papillomavirus in children prior to sexual debut has proven an efficient strategy against HPV related diseases including RRP. In this commentary, we review the recently published clinical characteristics of RRP cases in Zimbabwe. We also discuss the importance of adopting a quadrivalent vaccine against HPV types causing low risk HPV in Zimbabwe as a nationwide strategy against RRP in the population.

Main Text

As the year commenced, we released results on the Human papillomavirus (HPV) types causing Recurrent Respiratory Papillomatosis (RRP) in Zimbabwe[1]. To the best of our knowledge this is the first documentation of the clinical characteristics of RRP patients in Zimbabwe and the HPV types causing RRP. RRP is a rare benign disease of the respiratory tract characterised by a recurrent development of exophytic lesions with a connective stalk covered by epithelial cells. RRP has a strong predilection for the larynx[2,3,4] However, papillomas are known to progress to lower regions of the respiratory tract like the trachea and bronchial tree[5]. Affected children often suffer significantly during the active phase of the disease with recurrent hospitalisation for excisional surgeries to remove the growing tumours. Growing tumours, if left untreated, can lead to death through obstruction of the airways. Morbidity is considerable; long- term effects include scarring of the vocal chords, delayed speech development and when a tracheostomy is performed, muteness.

RRP is predominantly a bimodial disease presenting two different disease onsets. The first onset, called Juvenile onset of RRP (JoRRP) occurs in patients younger than five years of age; with 25% of the cases presenting in infancy[6]. The second onset called Adult onset of RRP (AoRRP)[7,8] occurs in the third and fourth decade of life. A third peak has been reported[6], occurring in the seventh decade of life, suggesting RRP may be trimodial. We report a median age of three years at onset of disease[1] with the oldest patient being fourteen years of age. We did not observe any cases of AoRRP.

Similar studies in Africa[7,9,10] report a higher incidence of JoRRP than AoRRP. A stark contrast to epidemiological characteristics of patients in Norway and Colombia who were predominantly AoRRP cases. It would appear RRP is a predominantly pediatric disease in Sub-Saharan Africa, including in Zimbabwe. This observation increases the advocacy of identifying children at risk of developing RRP with the aim of preventing disease onset or progression in cases where lesions formation has commenced.

Although other factors (host and genetic viral factors) can play a role in development of JoRRP; a triad of risk factors is generally accepted as the strongest risk factor of JoRRP in an infant[11]. This triad includes vaginal delivery, being a first born and having a teenage mother. In our study, 84.6% of the children were born vaginally with only one infant born via C section. The commonality of vaginal delivery in our setting catapults the risk of developing JoRRP in infants especially if other risk factors are present. Mothers aged 16-21 years constituted 44% of all mothers recruited in the study , with 25% of all mothers aged 16-21years at delivery. At least 55% of all children were first born children. Implying 25% of all the children recruited in the study were born vaginally to teenage mothers as first children. Such children are therefore at high risk of developing JoRRP, especially if the mother has additional risk factors such as a history of condylomata or genital warts at birth[12]. Using this triad in our clinical settings therefore can enable clinicians to swiftly identify infants at risk of developing JoRRP and hence institute preventive measures to arrest the disease prior to development or at early onset in these high-risk children.

HPV is an established etiological agent of RRP[3,13-17]. HPV has a predisposition for the stratified epithelia of cutaneous and mucosal surfaces. HPV infection, therefore, leads to the formation of warts in anogenital, cutaneous and respiratory regions. HPV genotypes are classified as high or low risk depending on their association with malignancies. Low risk HPV types 6 and 11 are well established HPV types involved in the etiology of RRP, accounting for more than 90% of cases[14,18,15,19]. HPV6 and 11 remain the predominant types found in RRP cases in Zimbabwe[1]. However, HPV DNA was present in only 66% of our biopsies versus at least 90% in previous reports[14,18-20]. In our view, this discrepancy can be attributed to challenges in handling and storage during shipping of specimens for genotyping . Resource limited settings, like our own, are often incapacitated in typing HPV in country and thus specimens require shipping to laboratories in better resourced environments. It becomes imperative that efforts be made in capacity building of HPV typing in an effort to minimise such challenges in the future. High risk HPV typing in Zimbabwe has since begun, owing to their link to both cervical and other anogenital cancers. It is our hope that by year end, typing of low risk HPV types will be fully operational. This will greatly reduce challenges associated with handling and shipping of specimens and enhance capacity building which in turn will improve both RRP clinical and research outcomes.

Prophylactic vaccines have been developed against HPV. They are marketed as either bivalent (against HPV 16 and 18)[21,22], quadrivalent (anti HPV types 6/11/16/18)[23] or nonavalent (against HPV types 6/11/16/18/31/45/52/58)[24]. Nationwide prophylactic vaccinations[25-28] have become highly effective public health strategies against HPV infections and HPV related cancers. In May 2018, the Zimbabwean government became the 8th African country to launch a nationwide HPV vaccination program targeting prebuscent girls, aged 10-14 years; before sexual debut. The program was motivated by the relatively high incidence of cervical cancer in the Zimbabwean female population. As such, a bivalent vaccine was chosen for this purpose. The effects of the vaccination program on the incidence of cervical cancer in Zimbabwe are still to early to detect. However, valuable lessons have been learnt with regards to HPV vaccination at national scale. Lessons have been learnt in factors affecting both vaccination coverage and adherence, attitudes of both the communities and health personnel towards HPV vaccination and the level of support the government can provide. Systems have also been set in place and capacity built that can be employed in future national vaccination programs that target HPV low risk types.

The gynaecology and public health specialists have successfully lobbied the Zimbabwean government to adopt the quadrivalent vaccine in the nationwide program targeting prebuscent girls. There is possible spin off in reduced incidence of RRP from these girls as they mature into motherhood. However, the otorhinolaryngology community in Zimbabwe needs to lobby vaccination of children identified as high risk for the development of JoRRP or their mothers prior to birth. HPV vaccination has also been documented as a possible therapeutic agent against RRP[29], where remission has been observed; although controversy still shrouds its use as a therapeutic agent in the treatment of RRP. Future research in larger multi-site cohorts may provide the much-needed answers in the management of RRP using commercially available quadri and nonavalent vaccines.

Closing Remarks

The report on the human papillomavirus types causing recurrent respiratory papillomatosis is the first report emerging from Zimbabwe. This report confirms the etiology of HPV types 6 and 11 in the pathology of RRP. The report also corroborates the higher incidence of juvenile onset RRP as compared to adult onset RRP in Sub Saharan Africa. The report provides strong rationale in the advocacy of

the adoption of quadrivalent vaccines as a strategy against HPV related malignancies in Zimbabwe.

Acknowledgements

The authors would like to acknowledge all the children and their families who took part in the study referenced in this commentary.

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