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Recurrent respiratory papillomatosis: Management challenges in a tertiary health institution

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Abstract
Background: Human papilloma virus types 6 and 11 have been implicated as the cause of Recurrent Respiratory Papillomatosis, which is the most common benign laryngeal neoplasm amongst children.
Objective: To report therapeutic dilemma and its implication among children in developing country.
Methodology: Clinical records of 28 patients who were prospectively recruited at the department of otorhinolaryngology of the Usmanu Danfodiyo University Teaching Hospital, Sokoto and followed up over a 12 years (2006-2017) were analyzed. They all had Endoscopic surgical extirpation of the lesion under general anaesthesia and histology of the specimen confirmed the diagnosis.
Results: A total of 28 cases were analyzed, 20 (71.4%) males and 8 (28.6%) females with an M: F ratio of 2.5:1. Age range is between 2 – 15 years with mean age of 6.8years. The highest incidence was 53.6% in patients within the age group of 1-5 years. Hoarseness was the commonest presenting feature 28(100%) followed by upper airway obstruction in 20(71.4%) necessitating emergency tracheostomy. All the patients had rigid endoscopic surgical excision of the lesion with no adjuvant therapy. In 23(82.1%) of patients, Vocal cords were the commonest site of the lesion.
Conclusion: There is a rise in the incidence of tracheostomy for recurrent respiratory papillomatosis in our region due to late presentation and this constitute a therapeutic dilemma. Surgery is still the mainstay of treatment to maintain adequate airway.

Keywords: recurrent respiratory papillomatosis, human papilloma virus, hoarseness, tracheostomy

Introduction

Recurrent Respiratory Papillomatosis (RRP) is a rare and benign neoplasm of the airway that carries a high morbidity [1]. This is because of its predilection for the larynx, the resultant airway obstruction and the recurrent nature of this condition [1, 2]. Human Papilloma Virus (HPV) causes it, mostly types 6 and 11 [3, 4]. These are also responsible for anogenital warts [5]. The more virulent types 16 and 18 of HPV may cause RRP rarely, but are mainly implicated in malignant conditions [1, 5]. Recurrent Respiratory Papillomatosis can be divided into a Juvenile Onset Recurrent Respiratory Papillomatosis (JO-RRP) and an Adult Onset Recurrent Respiratory Papillomatosis (AO-RRP) [6]. Reports by Derkay *et al* [1], showed an estimated incidence rate of 4.3 per 100,000 in JO-RRP and 1.8 per 100,000 populations in AO-RRP [1]. The JO-RRP is more aggressive, often presenting with multiple lesions that are recurrent requiring multiple surgical intervention, while the AO-RRP is less aggressive often presenting with single lesions with less propensity for recurrence [1, 3]. These also defer in their mode of transmission with JO-RRP being transmitted vertically, from a mother having genital warts to her child and AO-RRP being transmitted through Oro-genital contacts [2]. Reactivation of an earlier acquired dormant HPV infection may also be responsible for AO-RRP [1]. The recurrent and unpredictable character of this condition poses great challenge in its treatment especially in developing countries. No definitive cure has been identified for this condition and treatment is usually directed at relieve of airway obstruction by repeated surgical excision, avoidance of tracheostomy and the attendant risk of multiple exposure to General anaesthesia [1]. While different Lasers, Microdebriders and other powered instruments are now routinely used for excision of RRP in more developed settings because of their precision and safety, Cold Steel excision is still widely practiced in less developed settings [4,7]. Lasers have the advantage of achieving good haemostasis and working over longer distances, however the possibility of burns to underlying normal tissue and airway fire incidents are its drawbacks [8]. Microdebriders have the advantage of excision of lesions without injury to underlying tissue, at the same time removing excised tissue [9]. Inteferon, Intralesional Cidofovir and other Adjuvant treatments have been tried with varying degrees of clinical response [1, 9, 10]. The fact that this condition is common among the lower socio-economic class makes an already bad condition worse. Access to quality health care is difficult and even when this is available the ability of the caregivers to sustain treatment which may require multiple surgeries in a year, over many years is a challenge for those not on health insurance. This makes the patients to stay away from the hospital until their condition becomes severe, often presenting in upper airway obstruction. Emergency tracheostomy in some of these cases, even though undesirable may be inevitable. The introduction of quadrivalent HPV vaccine to Women of reproductive age has reduced the cases of anogenital warts, and generally increased the herd immunity against HPV in populations where the uptake of the vaccine is high [11].

It is expected that the reduction in anogenital warts in these women will reduce HPV transmission to their children, hence reducing the chances of developing RRP [1]. Promising results have been observed among younger children whose mothers had HPV vaccinations [1, 11].

However, because this is a rare disease, conclusions cannot be easily made. Quadrivalent HPV vaccine has also been used in persons with active RRP disease [1]. It has been shown to reduce the number of times a patient will need surgery, an indicator of recurrence [1]. This article aims to report the therapeutic dilemma and its implications among children in a developing country.

2. Materials and method

This was a retrospective study of all patients that presented to the ENT Department of Usmanu Danfodiyo University Teaching Hospital, Sokoto with Juvenile-onset Recurrent Respiratory Papillomatosis (JO-RRP) over a 12-year period (January 2006 to December 2017). Paediatric patients who were histologically diagnosed with RRP were recruited for the study. In our centre, usmanu Danfodiyo University Teaching Hospital Sokoto, surgical extirpation of the lesion is by cold steel method using cupped laryngeal forceps under general anaesthesia. Excluded from the study were patients whose medical records were not found or with incomplete clinical information and patients with Adult onset Recurrent Respiratory Papillomatosis (AO-RRP). Data extracted form patients clinical records included demographic characteristics such as age and sex. Other information included the main presenting symptoms, duration of tracheostomy and number of surgical interventions and follow up visits. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 23.

3. Results

A total number of 28 patients' records were retrieved. Out of these, 20 (71.4%) were Males, while 8(28.6%) were females, with a male to female ratio of 2.5:1. This study was conducted among patients aged 15 years and below, out of which 15 (53.6%) were between 1 – 5 years, 9 (32.1%) were between 6 – 10 years, while 4 (14.3%) were between 11 – 15 years of age [fig 1].

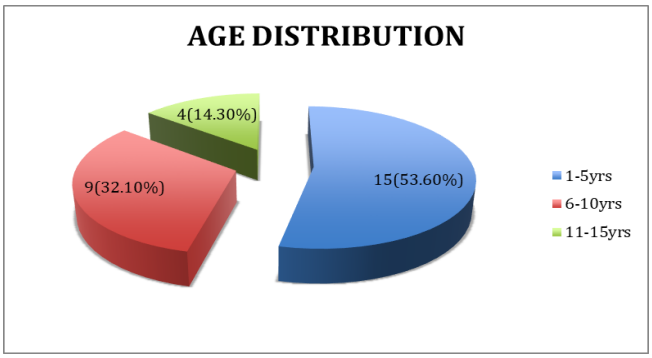

Fig 1: Age distribution.

All patients presented with hoarseness, and varying degrees of other symptoms [Table 1].

Table 1: Presenting Symptoms

S/No	Presenting Symptom	Number of patients	Percentage (%)
1	Hoarseness	28	100.0
2	Stridor	10	35.7
3	Upper airway obstruction	20	71.4
4	Cough	6	21.4
5	Dyspnea	2	7.1

All the patients had rigid endoscopic surgical excision of the lesion with no adjuvant therapy. In 23(82.1%) of patients, Vocal cords were the commonest site of the lesion.

All the patients 20(71.4%) that presented with upper airway obstruction had emergency tracheostomy, and were thereafter decannulated. The outcome and number of days taken to decannulate them is presented in [Table 2]. Recurrence occurred in 6(21.4%) of patients within two years while majority were lost to follow up.

Table 2: Duration before decannulation and outcome

S/No	Days before decannulation	Number of patients (%)	Outcome
1	1 – 5	4 (20)	Successful
2	6 – 10	15 (75)	Successful
3	11 – 15	1 (5)	Successful

Fig 2: Endoscopic view of RRP in the larynx of a 13-year-old boy.

4. Discussion

Morrell Mackenzie in 1880 first described JO-RRP a benign laryngeal lesion in children. In the 1990's, southern blot hybridization of HPV DNA in laryngeal papilloma confirms HPV types 6 and 11 as causative agents [12]. We had a male preponderance (71.4%) in this study with sex ratio of 2.5:1, is similar to previous studies in Nigeria [4, 7]. but at variance with reports from West African sub region[4]. Though JO-RRP has been observed to affect boys and girls nearly equally [6], studies have observed a male predilection even among children [4, 7, 11, 13, 14, 15]. Other authors observed a female preponderance among patients with JO-RRP [3, 16, 17]. The peak presentations of JORRP (53.60%) seen in this study were between 1 – 5 years of age. This agrees with the traditional age of presentation of JO-RRP [3, 13] and similar findings by some authors [4, 7, 16]. In contrast some authors reported higher mean age at presentation, these studies were carried out among both children and adults with no separate computation of their mean ages [4, 14]. We observed hoarseness as the predominant symptom among our patients. It is a well-established fact that because of its

predilection for the larynx, any small lesion on the vocal cord can distort the architecture of the cord and present early with hoarseness [5]. This make JO-RRP a strong differentials that must be considered in children with voice change. However, caregivers in our environment are unconcerned with hoarseness and keep the patients away from the hospital, preferring to seek medical care from non-otorhinolaryngologist until the child presents late with upper airway obstruction. Late presentation is one of the therapeutic dilemma encountered in the adequate management of JO-RRP in this study. Apart from patient factor in presenting late to physician, misdiagnosis of the clinical condition may contribute to the therapeutic dilemma found in this study. Even though JO-RRP has varied symptoms, majority of our patients has hoarseness, upper airway obstruction and stridor, which may arouse the possibility of papillomatosis in children. This emphasizes the importance of continue health education in understanding the symptomatology of this condition for prompt diagnosis. The availability of radiological investigations such as, computerized tomography scan (CT-Scan) and Magnetic resonance imaging (MRI) has enhance the accurate diagnosis of laryngeal papillomatosis, unfortunately it was not affordable to the patients thus a therapeutic dilemma for diagnosis. All patients in this study had plain x-rays soft tissue neck that complimented the symptomatology for diagnosis. We are reporting tracheotomy rate of 71.4% which is higher than studies done in west African subregion [4, 14]. This may be attributed to the late presentation with upper airway obstruction necessitating emergency tracheostomy that is undesirable but inevitable.

Even though tracheostomy should not be encouraged due to seeding of papilloma into the trachea, the huge financial burden involve in the management of this condition is a limitating factor in accessing medical care in time and this constitutes therapeutic dilemma in developing country. However extra laryngeal disease has not been reported in our series and no difficult Dec annulation observed in this study [Table. 3].

All our patients had Endoscopic excision of the lesions using Cold Steel method. Intraoperatively multiple grapelike polyps [fig. 2] was the commonest finding in this study and is similar to findings by other authors [4, 14]. Majority of our patients with tracheostomy had increase frequency of surgical extirpation of the papilloma and may be attributed to disease aggression not directly from the tracheostomy as reported by *Orji et al.* [7] Lasers, Microdebriders and other forms of powered Instrumentation are the more desirable methods of excision of RRP [9], but high cost and lack of proper maintenance of the few available ones has driven Surgeons in this part of the World to resort to the use of Cold Steel for RRP excision for most of their patients. This is because most patients that present to the hospital pay for healthcare out of pocket, and considering the number of surgeries the child may need, they are not able to sustain payment for surgery using Cold steel l *et al* one powered instrumentation. Pricing for surgery that will involve the use of laser or other powered instrumentation is usually higher than that of cold steel, because of high maintenance costs. None of the patients in this study had any form of Adjuvant therapy. Several Adjuvant therapies have been tried for the management of RRP with different responses yet none has 'cured' the condition [9]. Interferon, Intralesional Cidofovir, Bevacizumab and HPV vaccination as adjuvant treatment has been tried [1, 8, 9, 18, 19]. These Adjuvant therapies are not without their own problems [9, 18]. Interferon is one of the earliest adjuvant therapies used in treatment of RRP [8]. Its use has however been limited by its systemic side effects, thereby favoring intralesional adjuvants [8]. Murono *et al* offered intralesional Cidofovir only for 10 patients in Japan and observed an improvement in Derkay's severity score for all patients with complete resolution of symptoms in one patient [18]. Perhaps a combination of surgery with intralesional Cidofovir may yield different results. Cidofovir use for RRP is however off label and fought with complications like nephrotoxicity, neutropenia and possible oncogenic effects [18]. The uptake of HPV vaccination as a preventive strategy is on the increase [1, 20], however much more interesting is the use of HPV vaccination in patients with RRP. Peter Goon *et al* observed a more than seven fold decrease in the incidence rates of papillomatosis requiring surgical intervention following immunization [19]. The rise in antibody titer following HPV vaccination helps reduce the rate of recurrence following surgical excision [19, 21, 22]. The lack of access to these Adjuvant therapies and the uncertainties in its use has discouraged its application to patients in our environment. We observed a recurrence rate of 21.4%, which is a common finding in the management of laryngeal papillomatosis especially in patients infected with HPV (type 11) [18].

Majority of our patients were lost to follow up probably due to the natural history of recurrence of this condition resulting in multiple surgical extirpation, poor voice quality post operatively and the huge financial burden to parents or patient could be frustrating. There was no mortality recorded in our study.

5. Conclusion

Recurrent Respiratory Papillomatosis is a rare benign laryngeal lesion which can be life threatening. The therapeutic dilemma and its implication among children in developing country is multifactorial, they includes late presentation, misdiagnosis, inadequate diagnostic equipment, unpredictable and recurrent nature of the lesion, huge financial implications in the management of this disease and no definitive cure. In our region surgery is still the mainstay of treatment to maintain adequate airway. We therefore recommend the following:

1. Adequate funding of Health care institutions for the provision of affordable equipments.
2. Physician high index of suspicion of the symptomatology and the institution of appropriate treatment.
3. Continuing health education on early presentation of patients and discouraging tracheostomy.
4. More research on definitive treatment is hereby advocated.

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