

## A Retrospective Study of Recurrent Respiratory Papillomatosis in West Bengal, India

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**Abstract:** Recurrent respiratory papillomatosis is a rare benign disease of the upper airway caused by HPV, primarily affecting the paediatric age group. A retrospective analysis of 11 cases of recurrent respiratory papillomatosis was done in the present study extending for 30 years in three Medical Colleges of India. The presenting age of the patients was 2 to 7 years. Around 73% of recurrent respiratory papillomatosis cases had been diagnosed within 5 years of age. In our study, we did not find any case of adult onset recurrent respiratory papillomatosis and all the cases were of juvenile onset. Both males and females were affected equally with a male to female ratio of 1.2: 1. The incidence was more in the population with lower socio-economic conditions. Out of the total 11 cases, 6 patients required emergency tracheostomy for obstruction of the airway due to extensive involvement of the larynx. Microlaryngoscopic removal of the lesions with microdebrider was the primary treatment combined with adjuvant nonsurgical/medical treatments to contain the virus and growth of the tumours. In the case of the 5 (45%) patients presenting with hoarseness of voice without respiratory distress, complete microlaryngoscopic excision of the lesions were possible. However there were recurrences in 3 of these 5 cases, requiring further surgeries. In the case of the 6 (55%) patients, who required emergency tracheostomy for acute respiratory distress, complete microlaryngoscopic excision of the lesions were not possible in the first surgery, due to extensive pathology and there were recurrences in all these cases. Collectively, there were recurrences in 9 cases out of the total 11 cases. The recurrences occurred within 3 to 6 months and required 4 revision surgeries on an average. The incidence of recurrent respiratory papillomatosis has decreased gradually in the recent past due to improvement of hygiene and medical care. We did not find any case of RRP in the last 10 years. The quadrivalent HPV vaccine (GARDASIL) is effective in decreasing the prevalence of recurrent respiratory papillomatosis. There is sparsity of data of recurrent respiratory papillomatosis in the Indian subcontinent and it is suggested that sufficient epidemiological data should be accumulated to characterize the disease, as in Western countries.

**Keywords:** RRP, recurrent respiratory papillomatosis, HPV, human papilloma virus, quadrivalent vaccine.

### INTRODUCTION

Sir Morrell Mackenzie (1837–1892) [1] first recognized papillomas as a lesion of the laryngo-pharyngeal tract in children in 1871. Recurrent respiratory papillomatosis (RRP) is a rare disease, presenting as a recurrent proliferation of benign squamous cell papillomas in the larynx as well as in the other parts of the aero-digestive tract. Over 90 % of these tumours are due to throat infection caused by low risk strains of human papilloma virus (HPV 6 & 11) [2]. Larson and Derkay [3] characterised recurrent respiratory papillomatosis (RRP) as juvenile onset

recurrent respiratory papillomatosis (JORRP) or adult onset recurrent respiratory papillomatosis (AORRP) on the basis of diagnosis before or after 12 years of age, respectively.

Juvenile onset recurrent respiratory papillomatosis is usually thought to be vertically transmitted to the child during birth from an infected mother, although placental transmission has also been reported [4]. The cause of adult onset recurrent respiratory papillomatosis is unknown, but sexual transmission is suspected. Auburn [5] in his study found

that males have a higher risk (4-fold) when compared to females, in developing adult onset recurrent respiratory papillomatosis. Recurrent respiratory papillomatosis usually develops at the junction between squamous and columnar epithelial cells, such as vocal cords, subglottis, laryngeal surface of epiglottis, and trachea. One of the factors associated with the development of recurrent respiratory papillomatosis is altered immune response to HPV proteins [6]. As pregnancy has been found to enhance disease progression, hormonal factors are also thought to be involved in the pathogenesis of recurrent respiratory papillomatosis. Recurrent respiratory papillomatosis has proved to be a major clinical problem because of its location, often dramatic presentation due to significant airway obstruction, the ongoing resistance to therapies, high frequency of relapses, tendency of spreading to the lower respiratory tract and oesophagus (aggressive forms), and the possibility of malignant transformation into squamous cell carcinoma. The morbidities associated with any form of recurrent respiratory papillomatosis are mainly due to airway obstruction and the use of procedures and multiple drug regimens necessary to deter the growth of the papillomas [5]. The tumours may lead to narrowing of the airway, which may cause change in voice or airway obstruction. Laryngeal papillomatosis is initially diagnosed by indirect laryngoscopy by observing warty growths in the larynx and can be confirmed by a biopsy. The incidence of recurrent respiratory papillomatosis has been estimated at about 1.8 per 100,000 in adults and 4.3 per 100,000 in children [7].

HPVs affecting the mucosal tracts can be broadly divided into high-risk and low-risk types, based on their ability to cause malignant transformation of epithelial cells. High-risk types HPV-16 and HPV-18 are most commonly associated with cervical cancers as well as a subset of oropharyngeal carcinoma [8]. HPV-6 and HPV-11 account for most of the cases of recurrent respiratory papillomatosis and are considered as low-risk subtypes, typically not associated with malignancy [9]. In recurrent respiratory papillomatosis, HPV-11 infection is more common and the disease presents a more aggressive clinical course in comparison to HPV-6 [10]. Rarely, recurrent respiratory papillomatosis is caused by HPV types 16, 18, 31, and 33 [11].

**MATERIALS AND METHODS**

This study was conducted over a period of 30 years in three Medical Colleges in West Bengal, India. The subjects of this study were selected from the patients presenting with hoarseness of voice in the E.N.T. outpatient department of these hospitals. All

these patients were examined and only the cases with hoarseness of voice for more than 15 days were selected. The patients presenting with other voice disorders were excluded from this study. The patients with hoarseness of voice for less than 15 days were also excluded. During the initial phase of our study, indirect laryngoscopy was done in all cases and conventional direct laryngoscopy was done wherever needed. This was later combined with regular fibre optic laryngoscopy upon availability of the instruments required.

Proper history was taken in all cases, with special importance to age, sex, occupation, socio-economic status, complaints with duration, and predisposing factors. The onset and the progress of the symptoms were noted. Past history of similar episodes and other illnesses and history of previous treatment were taken. Routine haematological assessment including total leucocyte count, differential leucocyte count, haemoglobin, and erythrocyte sedimentation rate were done in all cases. Biochemical estimation of blood sugar, blood urea, and routine examination of urine were carried out in all patients. X-ray chest PA view was done in all cases and x-ray soft tissue neck, AP and lateral views were taken, where required.

Some patients directly came to the emergency of these hospitals with acute respiratory distress. They had been admitted in the ENT wards directly and provisionally been diagnosed to be suffering from recurrent respiratory papillomatosis. They were also included in our study.

Total 11 cases which were clinically diagnosed as recurrent respiratory papillomatosis were included in our study. Necessary surgery was done and the tissue samples were sent for histopathological examination in all cases. Separate samples were sent for HPV testing also. After the surgery, absolute rest of voice was advised for one week. Voice therapy was advised and the patients were followed up for recurrences.

**RESULTS AND DISSCUSSION**

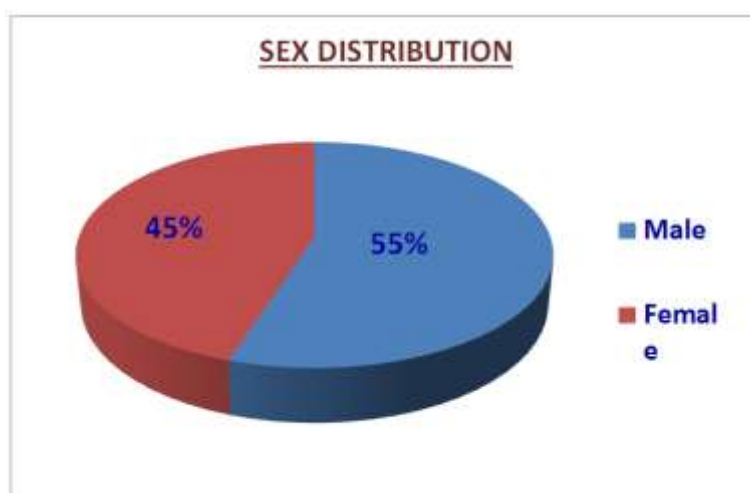
In our study, the age of the patients was ranging from 2 to 7 years. We observed that around 73 % of the juvenile onset recurrent respiratory papillomatosis cases had been diagnosed within 5 years of age. Larson and Derkay [3] also observed that the majority (75%) of the juvenile onset recurrent respiratory papillomatosis patients were diagnosed by 5 years of age.

**Table-1: Age distribution of patients**

Age groups	Number of cases	Percentage (%)
1-5 years	8	72.7%
5-10 years	3	27.3%
Total	11	100%

Derkay [7] observed that the incidence of RRP in the United States was 1.8 per 100,000 in adults and 4.3 per 100,000 in children. In our study, we did not find any case of adult onset recurrent respiratory papillomatosis. Mishra *et al.* [12] expressed their concern over the sparsity of data of recurrent respiratory papillomatosis in the Indian subcontinent and suggested the need for accumulating sufficient epidemiological data to characterize the disease as in Western countries.

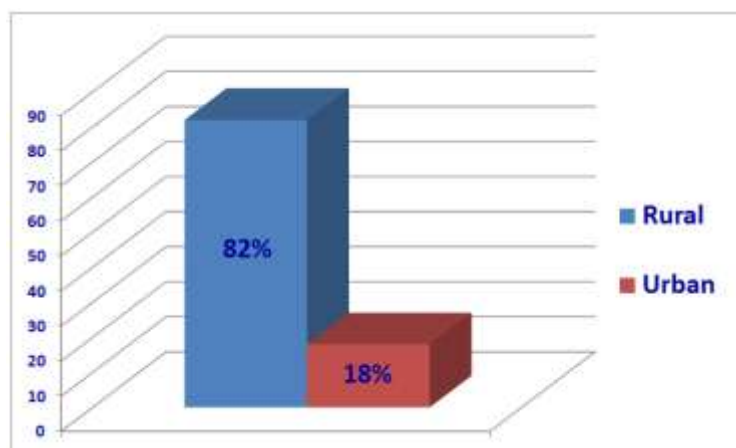
In our study, we found that out of the 11 patients, 6 (55%) were males and 5 (45%) were females with a male to female ratio of 1.2:1. We did not observe any significant difference in the incidence in male and female. Baidoo & Kitcher [13] in their study of 69 patients found 33 male patients and 36 female patients, with male to female ratio of 1:1.1. Their observation was similar to the observation made in our study that juvenile onset recurrent respiratory papillomatosis affected both male and female equally.



Pie Chart showing sex distribution of patients

In our study, we found that 9 patients (82%) were from rural area and 2 patients (18%) were from urban area. The difference between the incidence in

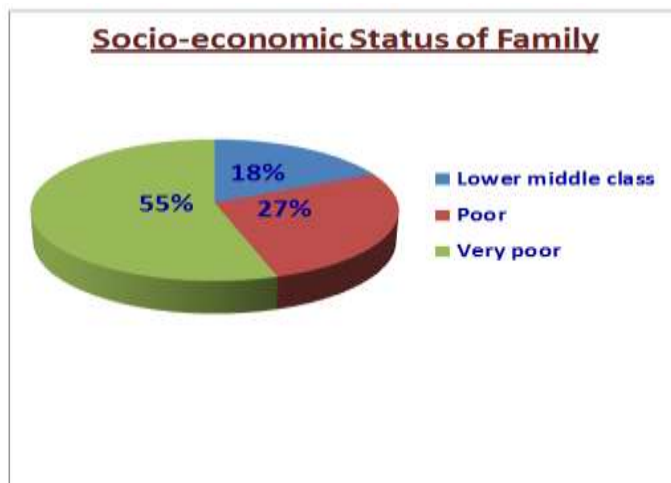
rural and urban areas was significant. This could be attributed to the lower socioeconomic condition and lack of hygiene in the rural areas.



Bar diagram showing residential distribution of patients

In our study, we found a significant correlation between the socioeconomic status and the incidence of recurrent respiratory papillomatosis. Out of the total 11

cases, 6 (55%) patient's belonged to very poor families, 3 (27%) patients belonged to poor families, and 2 (18%) patients belonged to lower middle class families.



Pie diagram showing relation of RRP with socio-economic status

Leung *et al.* [14] in a cross-sectional study of all active juvenile onset recurrent respiratory papillomatosis patients from the Hospital for Sick Children in Toronto, Canada, found that nearly half of the patients were below the poverty line. Marsico *et al.* [15] in a pilot study of a large database of publicly and privately insured patients in the United States, consistently found that incidence of recurrent respiratory papillomatosis was higher in publicly insured patients in comparison to those with private insurance, 3.21 vs. 1.98 per 100,000 respectively. They explained that patients with public insurance came from a lower socioeconomic level than those with private insurance. Those findings corroborated with our findings that patients of lower socioeconomic status were at increased risk. However, no correlation had been found between socioeconomic status and severity of the disease as was also observed by Hartley *et al.* [9].

In our study of 765 cases with hoarseness, the incidence of recurrent respiratory papillomatosis was 1.4% (11 cases). Soni *et al.* [16] in their study found the incidence of respiratory papillomatosis as 7.78% among the patients presenting with hoarseness. We found all the cases in the first 20 years of our study. No case of recurrent respiratory papillomatosis had been found by us in the last 10 years. This could be attributed to the

improvement of hygiene and medical care in the recent years.

All our patients had no manifestation of recurrent respiratory papillomatosis immediately after birth, in spite of being infected either before or during birth. Larynx was the most common site of infection noted in children in our study and therefore all the symptoms we found were due to its involvement. First symptom noted by parents was either altered cry, in case of very young patients, or change of voice in older ones. Because of the subtle nature of the symptoms, the parents did not give much importance to that. Other manifestations due to involvement of the respiratory system were recurrent upper respiratory tract infections, chronic cough, dyspnoea, pneumonia etc. [11].

In all the cases, papillomas were seen as multiple, white to pinkish growths with a lumpy texture similar to a cauliflower (Fig. 1). In our study, papilloma growths were seen on the vocal folds and in the space above the vocal folds. The growths had a tendency to spread to other parts of the of aero-digestive tract and had a predilection towards the junctions of squamous and ciliated columnar epithelium or the tissue junctions arising from injury.



**Fig-1: Microlaryngoscopic picture of RRP with synechia formation over the anterior commissure resulting from previous surgery**

Out of the total 11 cases, 6 cases came to the emergency of these hospitals with acute respiratory distress due to airway obstruction resulting from extensive involvement of the larynx. We had to perform emergency tracheostomy in these cases to relieve their respiratory distress. In all the 11 cases, microlaryngoscopic surgery was done to remove the

papillomas. For confirmation of the diagnosis, biopsy samples were sent for histopathological examination. Samples were sent separately for HPV testing. Histopathological picture comprised of benign lesions having papillomatous projections of non-keratinized squamous epithelium with central vascular cores (Fig. 2).



**Fig-2: Histological picture of RRP showing papillomatous projections of non-keratinized squamous epithelium with central vascular cores. (x80)**

Surgical excision aimed to secure an adequate airway and an acceptable quality of voice. In the case of the 5 (45%) patients presenting with hoarseness of voice without respiratory distress, complete microlaryngoscopic excision of the lesions were possible. However there were recurrences in 3 of these cases requiring revision surgeries but tracheostomy was never necessary. In the case of the 6 (55%) patients, who required emergency tracheostomy, complete microlaryngoscopic excision of the lesions were not possible in the first surgery, due to extensive pathology and there were recurrences of the lesions in all these cases. Collectively, there were recurrences in 9 cases out of the total 11 cases. The recurrences occurred within 3 to 6 months of the first surgery and required further surgeries. On an average, 4 revision surgeries were necessary in each case. De-cannulation of the

tracheostomies was done after one year of recurrence-free period in the patients who had undergone tracheostomies. We followed up all the patients closely up to the age of 25 years and found no further recurrences.

The cumulative tracheostomy rate in our study was 55%, which was lower than 70% as observed by Nwaorgu *et al.* [17] in their study. Tracheostomy should be avoided as much as possible, as the trachea may serve as a pathway for spreading the disease down to the tracheo-bronchial tree. The use of microdebrider in microlaryngel surgery for recurrent respiratory papillomatosis has proved to be an important tool for precise as well as selective removal of the papillomas while relatively sparing unaffected tissues. We used microdebrider in 4 cases, which were diagnosed after



the availability of the instrument in our hospital. In addition to the lower risk of complications, surgery using microdebrider was found to be less expensive and less time consuming. It also resulted in a better outcome in terms of voice improvement in the post-operative period.

Surgery alone may not be sufficient to control the recurrent respiratory papillomatosis in all cases. Adjuvant medical/nonsurgical treatments are found to be useful in such cases. These therapies however are not sufficient to cure recurrent respiratory papillomatosis alone and are found to be only supplementary to surgical removal. Adjunct medical/nonsurgical treatments aim at containing the virus and growth of the tumours. They include indole-3- carbinol or its dimer diindolylmethane, interferon, and photodynamic therapy [5]. Other modes of nonsurgical treatments tried in various clinical trials include antiviral drugs like cidofovir, ribavirin, and acyclovir. Carbon dioxide LASER has also been used for the removal of papillomas. However, LASER surgery has its own separate risks, and has been associated with a higher incidence of respiratory tract burns, stenosis of airway, severe laryngeal scarring, and tracheo-oesophageal fistula.

In a multicenter study comparing surgery alone versus surgery with adjuvant IFN- $\alpha$ , Healy *et al.* [18] observed an initial decrease in disease progression at 6 months in the later case. However, this effect did not persist after 2 years. No benefit was observed from the use of IFN- $\alpha$  alone. Venkatesan *et al.* [19] suggested prolonged use of IFN- $\alpha$  only if a positive response is noted. However, treatment should be stopped if no response is noted or toxicity develops. Although its exact benefit is unpredictable, IFN- $\alpha$  may be considered for adjuvant therapy for recurrent respiratory papillomatosis, on the basis of the initial response we get from the treatment.

The most interesting and promising recent development in this area is the quadrivalent HPV vaccine. Currently, a bivalent vaccine designed against the L1 capsid proteins of HPV-16 and HPV-18 and a quadrivalent vaccine with activity against HPV-6, HPV-11, HPV-16, and HPV-18 are available. The bivalent vaccine is used to prevent cervical cancer but does not address HPV-6 and HPV-11, which are the most common causes of RRP. HPV infection seems to be as common in men as in women but is often asymptomatic in men. This contributes to the high rate of transmission between sexual partners [20]. The quadrivalent vaccine (GARDASILTM; Merck and Co., Inc., Whitehouse Station, NJ, USA) is approved for administration in young female teenagers as well as young boys and is currently licensed by the FDA for the prevention of cervical cancer, adenocarcinoma in situ, intraepithelial neoplasia grades 1–3, vulvar and vaginal intraepithelial neoplasia grades 2–3, and genital warts

associated with HPV 6, 11, 16, and 18. While both, males and females are benefited from vaccination [21], it is uncertain what effect this will have on neonatal transmission of HPV or on the overall incidence of RRP.

Forster *et al.* [22] used the quadrivalent vaccine to treat a two year old boy with severe JORRP. The boy's condition was stabilized after the third immunization and no surgery was needed for 10 months. Young *et al.* [23] conducted a retrospective chart review of 20 RRP patients treated with Gardasil and reported that 13 (65%) out of 20 patients had complete or partial remission, with a 3.1 month increase in the time between surgical interventions. Furthermore, HPV vaccines, including the newly developed nonavalent Gardasil-9 have shown therapeutic benefit, but randomized clinical trials are needed to evaluate the efficacy of HPV vaccines to reduce the recurrence rate of RRP [24].

Current trends indicate that wide spread vaccination of pre-adolescent females with HPV vaccine will further decrease the incidence of genital wart. This is expected to reduce the incidence of secondary laryngeal infection to newborns via vertical HPV transmission and in turn reduce JORRP and overall RRP incidence [25].

Other preventive measures which we can consider intuitively, is adopting caesarean section to reduce the risk of vertical transmission of HPV in mothers with active condylomata. However, Kosko and Derkey [26] suggested that due to uncertainty regarding intra-partum exposure and insufficient evidence to support effectiveness of caesarean section in preventing vertical transmission, all pregnant women with condylomata, should not undergo caesarean section, which is associated with a higher morbidity and mortality for the mother and a much higher economic cost. This option should only be chosen after proper discussion with the at-risk mother by her obstetrician explaining the risks and benefits of the procedure in her particular case.

## CONCLUSION

Recurrent respiratory papillomatosis is a rare benign disease of the upper airway caused by HPV, primarily affecting paediatric age group. In spite of being infected either before or during the birth, the presenting age of the patients was 2 to 7 years due to the subtle nature of the disease. There was no significant difference in the incidence of JORRP in males and females. The incidence was more in the population with lower socio-economic conditions. Microlaryngoscopic removal of the lesions with microdebrider was the primary treatment combined with other adjuvant nonsurgical/medical measures where necessary.

Recurrent respiratory papillomatosis is relatively rare in the Indian subcontinent and its incidence has reduced gradually in the recent past due to improvement of hygiene and medical care. The most promising recent development in the control of RRP is the quadrivalent HPV vaccine (GARDASIL). Intuitive, adoption of caesarean section to reduce the risk of vertical transmission of HPV in mothers with active condylomata should only be opted after proper discussion between at-risk mother and her obstetrician.

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