NO ASSOCIATION OF RECURRENT RESPIRATORY PAPILLOMATOSIS AGGRESSIVENESS AND HUMAN PAPILLOMA VIRUS TYPE 6 AND 11

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Research Report

NO ASSOCIATION OF RECURRENT RESPIRATORY PAPILLOMATOSIS AGGRESSIVENESS AND HUMAN PAPILLOMAVIRUS TYPE 6 AND 11

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ABSTRACT

Recurrent Respiratory Papillomatosis (RRP) is the most common benign neoplasm of the larynx among children as a result of HPV infection mainly type 6 and 11. RRP is still considered as serious problem since papilloma in the airway can cause hoarseness and obstruction which later described as aggressive and non aggressive types. Patients underwent multiple surgeries to keep airway patency and in order to communicate vocally. Previous studies reported that HPV-11 was associated with a more aggressive disease course. This study aim is to determine the association of RRP aggressiveness with HPV-6 and 11. Papilloma specimens were taken from patients who underwent surgical treatment of RRP patients and subjected HPV typing. All 17 patients with completed data and epidemiologic questionaires were defined for their staging to disease severity. Informations in the database were analyzed to identity statistically significant relationship with HPV type and knowing the HPV type is to predict the disease course. 17 patients RRP (12 males and 5 females) with age at onset 3,15 + 2,28 years and age at diagnosis 3,81 + 2,51 years. Surgery was performed 2,71 ± 1,16 times per year and 9 patients treated more than 3 surgeries per year. 10 patients had distal papilloma and 11 patients had tracheotomy. Agrressive disease was show found in 14 patients among 17 patients. HPV-11 was detected in 10 patients, HPV-6 was detected in 7 patients. According to the statisitcal analysis (Chi square test), there is no relationship between HPV type and disease aggressiveness. HPV-6 and 11 are not the only cause that affect the aggressiveness of Recurrent Respiratory Papillomatosis.

Keywords: *Papilloma, recurrent papillomatosis, respiratory papillomatosis, human papilloma virus, juvenile papillomatosis, adult papillomatosis*

ABSTRAK

Papiloma Saluran Pernapasan Berulang (PSPB) merupakan salah satu neoplasma jinak pada laring yang paling sering ditemukan pada anak sebagai hasil infeksi Human Papillomavirus khususnya tipe 6 dan 11. PSPB masih dianggap sebagai masalah serius karena papiloma pada saluran pernapsan dapat menyebabkan suara parau dan lebih lanjut menyebabkan obstruksi jalan napas, sehingga dikatagorikan sebagai penyakit agresif dan tidak agresif. Penderita dapat menjalani operasi beberapa kali untuk menjaga patensi jalan napas dan untuk memperbaiki kualitas suara. Studi terdahulu melaporkan bahwa HPV-11 memiliki hubungan dengan perjalanan penyakit yang agresif. Penelitian ini bertujuan untuk menentukan hubungan agresivitas PSPB dengan HPV tipe 6 dan 11. Diharapkan identifikasi tipe HPV dapat menjadi prediksi perjalanan penyakit. Spesimen papiloma didapatkan saat penderita PSPB menjalani pembedahan dan seluruhnya diperiksa tipe HPV. Didapatkan 17 penderita memiliki rekam medik dan kuesioner yang lengkap sehingga dapat ditentukan derajat keparahan penyakit. Informasi dikumpulkan dan kemudian dianalisis untuk mendapatkan hubungan yang bermakna dengan tipe HPV. 17 penderita PSPB (12 laki-laki dan 5 perempuan) dengan usia saat onset gejala 3,15 + 2,28 tahun dan usia saat diagnosis 3,81 + 2,51 tahun. Jumlah total operasi tiap tahun 2,71 ± 1,16 kali dan 9 penderita diantaranya menjalani lebih dari 3 kali pertahun. 10 penderita memiliki implantasi papiloma distal laring dan 11 penderita pernah menjalani trakeotomi. Penyakit yang agresif didapatkan pada 14 dari 17 penderita, dan HPV-11 didapatkan pada 10 penderita. HPV-6 didapatkan pada 7 penderita. Uji statistik menunjukkan tidak ada hubungan antara tipe HPV dengan agresivitas penyakit. HPV-6 dan 11 bukan menjadi satu-satunya faktor yang mempengaruhi faktor agresivitas penyakit

Kata kunci: *Papilloma, papillomatosis rekuren, papillomatosis pernapasan, virus papiloma manusia, papilomatosis remaja, papilomatosis dewasa*

INTRODUCTION

Human papillomavirus type 6 and 11 are the most important etiologies of RRP by expressing gene E6 and within the cell and contribute in oncogenesis. Protein E6 plays a role in binding and deactivating protein p53, whereas protein E7 will bind pRb. These HPV types differ in affinity to bind protein p53 and pRb.[1,2]

Recurrent Respiratory Papillomatosis or RRP is a disease caused by HPV type 6 and 11 that manifest as papilloma growths in respiratory tract and characteristically recurrent. There are two types of RRP, child onset or juvenile type (*juvenile onset* RRP/JORRP) and adult onset or adult type (*adult onset* RRP/AORRP). Juvenile has onset peak at age 2 – 4 years and grow aggressively, whereas adult type has peak incident at age 20 – 40 years.[3]

In United States, RRP incidents in child population estimated are 4,3 cases per 100 thousands children and 1,8 cases per 100 thousands adults. New incidents reported 80 to 1500 cases per year with prevalent rates of 700 to 3000 active cases in year 1999.[4] At 1997, we have 57 new patients, 82% were below 10 years old. Still in Dr. Soetomo hospital, we have 21 new patients of 51 total cases between 2006 to 2010, with common proportion on both gender.

RRP is diagnosed by clinical symptoms, endoscopic examination and histopathology.[5,6] Stridor and persistent or progressive hoarseness accompanied shortness of breath are the main symptoms.[7] Other rare symptoms are chronic cough, recurrent pneumonia, and failure to thrive.[8,9] Vocal cord is the initial and most common sites for papilloma growth thus hoarseness is the main symptom.[10] Endoscopy is the main examination method for definitive diagnosis.[9] Final confirmation is done by tissue histopathology examination.[5]

This disease can be both non aggressive which resulting a remission, or more aggressive that require repetitive surgery.[3] Aggressive type characterized by recurrent papilloma growth in more than one site. The most common sites are oral cavity, trachea and bronchus. The criterias according to Buchinsky[11] include total surgical histories, distal site of papilloma, and history of tracheotomy procedures.

Aggressive disease was classified based on its surgical requirement more than 10 times, three or more surgeries within a year, and papilloma involvement in subglottic area. Criterias of non aggressive are based on surgical requirement less than 10 times, not exceed 3 surgeries within a year, and no subglottic involvement. This degree of severity will assist the identification of prognosis.[10]

Yusuf[8] reported 75% RRP patients that need tracheotomy due to upper airway obstruction. Rachmawati[6] found 11 of 51 patients (21,57%) had tracheal and bronchial involvements. Thirty of 51 patients (70,59%) had tracheotomy histories, and 8 of 37 juvenile type RRP patients 21,62%) had 3 or more MLS procedures (microscopic laryngeal surgery) within a year.

MATERIAL AND METHOD

The study procedures are mention as followed. All RRP patients who visit the ORL-HNS OPD and ward of Dr. Soetomo hospital for MLS schedules were informed about the purposes and procedures of study (informing consent). Patients/parents approval were asked by sign the informed consent. In ward they were interviewed by questionnaires and their medical records from OPD were analyzed. Patients then categorized become aggressive or non aggressive group. The tissue from MLS is the study sample. The speciments were sent to LPT UA for HPV-6 and 11 examinations by PCR method.

Criterias of aggressive RRP consist of three or more papilloma removal surgeries within a year, history of tracheotomy, or papilloma implantation in distal part of larynx (trachea or bronchus) by rigid or flexible bronchoscopy.[11]

Criterias of non aggressive RRP consist of less than three times papilloma removal within a year, never had tracheotomy, and no papilloma implantation in distal part of larynx (trachea and/or bronchus) by rigid or flexible laryngoscopy.[11]

Inclusion criterias are RRP patients in all age with complete medical record data along medication, and agree to join this experiments (informed consent). Exclusion criterias are patients with history ajuvan therapy within 30 days and not enough speciments biopsy for PCR examination.

RESULT AND DISCUSSION

There were total 17 juvenile type of RRP patients who had visit Dr. Soetomo hospital. All had completed data from when they were first diagnosed until their latest visit. Aggressive papilloma found in 14 patients (82,4%), whereas 3 patients (17,6%) categorized as non aggressive RRP.

The youngest onset was 0,5 year and the oldest was 8 years, with *mean* 3,15 ± 2,28 years and *median* 3 years. The ages when it were diagnosed ranged from 0,5 to 9 years with *mean* 3,81 ± 2,51 years and *median* 4 years. The range from onset of symptoms untill diagnosis establishment was 1 to 30 months with is *mean* 8,16 ± 10,88 months.

Clinical Progress

Hoarseness the most common symptoms in patient's first time visit a number of 9 patients (52,9%), whereas shortness of breath have been 8 patients (47,1%) as shown in Table 1.

The most frequent number of surgery within a year were 6 times and the less frequent number was 1 time, with *mean* 2,71 ± 1,16 times and *median* 2 times. Distal laryngeal papilloma were found in 11 patients (64,7%), whereas 6 patients (35,3%) had no distal laryngeal papilloma.

Tracheotomy histories were found in 13 patients (76,5%), whereas 4 patients (23,5%) had no tracheotomy histories.

Association HPV and number of surgery in 12 months, distal papillomas, and tracheotomy show no significan. Human papillomavirus type 6 found in 7 patients (41,2%) and 10 patients (58,8%) were infected by HPV-11. Aggressive RRP consist of 5 patients with HPV-6 (71,4% of total HPV-6 patients) and 9 patients with HPV-11 (90% of total HPV-11 patients). Non aggressive RRP consist of 2 patients with HPV-6 (28,6% of total HPV-6 patients) and 1 patients (33,33%) of HPV-11 patients. Fisher's test resulted p value 0,537 as shown in Table 2.

The result of age of disease onset in this study is showed no significant different from the previous studies. Wiatrak[12] reported the age when they were diagnosed ranged from 0,33 to 12 years, with *mean* 44 moths (3,67 years). Buchinsky[11] reported 3 years *median* which range from 0,1 to 13,1 years. Campisi[13] was found *mean* 4,4 years which range from 0,1 – 14 years. It suggests that papilloma growth will reach peaks at age three years. HPV takes time to multiplicate and affect the infected cells tissue to grow larger. It also shows the difference between papiloma with other congenital laryngeal disease. Congenital malformation of the larynx will cause symptoms immedieatly after birth.

Table 1. Summary data for 17 patiens with RRP were included in this study

Gender	Male = 12 (70,6%), Female = 5 (29,4%)
Birth order	first = 11 (64,7%), the others = 6 (35,3)
Maternal condyloma	yes = 2 (11,8%), no = 15 (88,2%)
Method of delivery	pervaginam = 17 (100%)
Maternal age	< 20 y = 1 (5,9%), š 20 y = 16 (94,1%)
Age at onset symptom	mean = 3,153±2,283 years, median = 3 year
Age at diagnosis	mean = 3,812±2,512 years, median = 4 year
Gap between symptom and diagnosis	mean = 0,659±0,907 years
Main complain at onset	Dsypnea = 8 (47,1%), hoarsness = 9 (52,9%)
Number of surgeries	š 3x = 9 (52,9%), < 3x = (47,1%)
Max number of surgeries in 12 months period	Median = 2x, mean = 2,71x, range = 1-6x
Agressiveness of course	Agressive = 14 (82,4%), indolen = 3 (17,6%)
Distal involvement	Yes = 11 (64,7%), no = 6 (35,3%)
Tracheotomy	Yes = 13 (76,5%), no = 4 (23,5%)
HPV type	6 = 7 (41,2%), 11 = 10 (58,8%)

Table 2. Crosstabulation HPV type and disease agressiveness

HPV type	Agressivness		P
	Yes	No	
6	5	2	
11	9	1	.537

This study is showed the time break from onset of symptoms until when it was first diagnosed. The *mean* was 8,16 ± 10,88 months range from 1 to 30 months. Patients were for examination when the symptoms first occurred and diagnosis were confirmed at the same time. But, it contrast to our country. Patients often postponed seeking medical facility when hoarseness as early symptoms of laryngeal papilloma appeared. Hence there were delayed diagnosis. Good health facilities are still not evenly distributed in some areas in Indonesia. This would postpone the therapy.

Shortness of breath due to airway obstruction and hoarseness are the main symptoms that cause patient to seek medication for the first time, it have almost equal percentages, hoarseness in 9 patients (52,9%) and shorness of breath in 8 patients (47,1%). These describe why the RRP patients visit in late phase hence patients often came with shortness of breath.

The early symptom of laryngeal papilloma are hoarseness and shortness of breath. These symtoms are the late signs due to their growth in the larynx. These symptoms support the data that there is the time break between time of diagnosis and onset of symptoms. The patients excuse their delay to medical facility due to their assumption that hoarseness was not a dangerous anomaly. The parents decide to postpone to check their children. The other reason for this delay was patient seek for alternative medication, problem in financial and transportation to the refferal hospital. Campisi[13] was reported that the percentage of hoarseness as the most common symptoms when it first diagnosed (80%), while stridor and respiratory distress are 30% and 23% respectively.

RRP have tri-symptoms that consist of progressive hoarseness, stridor, and airway obstruction. Hoarseness is the common and early symptoms in young children that indicate structural and functional anomalies of larynx. Vocal cord is the most common and initial sites of papilloma lesion. Hoarseness could appeared due to small lesion and become the early symptoms, however in the distance lesion this hoarseness could appear as late symptom. In addition to cause hoarseness, papilloma also resulting stridor or obstruction, depend on size of lesion.

Generally, the surgical indication is to aim maintain airway patency in order to avoid airway obstruction. Other indication including improving communication quality by preserving laryngeal structure to produce adequate voice. The m*ean* ± SD was 2,71 ± 1,16, median 2 times which range from 1 to 6 times. Buchinsky[11] was reported the number of surgery within 12 months period with median 4 times which range from 1 to 52 times. This value was bigger compared to this study result with median 3 times which range from 1 to 6 times. As patients arrive in our hospital in late condition and requires a tracheotomy, the often postpone the laryngeal surgery to remove the papilloma. That causes longer operation interval in this study.

Definitive therapy to eradicate RRP effectively remains unavailable. The present standard therapy is Micro Laryngeal Surgery (MLS) to remove papilloma

mass for maintaining airway patency and normal laryngeal anatomy structure. The progresses of the disease including spontaneous remission, or constant which need repetitive surgeries, and or become more aggressive that yet need surgery every few days to weeks. Aggressive disease need more frequent MLS to avoid airway obstruction.

The concept of disease aggressiveness involve some parameters, including papilloma growth, surgery frequency, total number of surgery, the need for adjuvant therapy and tracheotomy, and lower airway tract complications. These parameters related to some factors including onset in younger ages, HPV-11 infection, the need for tracheotomy, cigarette smoke exposure and poor response to *interferon*-α therapy.

Percentages of papilloma that grow in distal larynx is 64,7% and tracheotomy history is 76,5%. It showed that most of patients had aggressive type. That number identical with This reports were showed higher result compared with Wiatrak[12] who reported 11% tracehotomies and 23,3% distal papilloma growth. Buchinsky[11] was reported 10% tracheotomy histories and 25% with distal growth, while Campisi[13] was reported distal growth about 5,6% dan tracheotomies 2,8%. The more aggressive type of disease that found in this study seen by many distal papilloma growth incidents and tracheotomies. Tracheotomy will induced the distal implantation of papilloma or spreading to the lower airway include the trachea or even bronchial tree.

RRP is a rare disease with slow progressivity, some cases remain undetected until airway obstruction were occurred. The most common sites are oral cavity, trachea and bronchus. Distal implantation also can be triggered by jet ventilation during MLS.

Tracheotomy is one of the most frequent procedures in RRP patients in late condition although it could activate or trigger the spread of papilloma implantation in the distal larynx. Continued tracheotomy and sub glottic papilloma during tracheotomy would increase the risk of tracheal spread. The experts had agreed that tracheotomy should be avoided unless it was extremely required, and immediate decanulation should be performed soon after mass removal via MLS. Children with prolonged endotracheal tube could also increase the risk of papilloma growth through lesion mechanism that disrupts the respiratory mucosal continuity thus cause papilloma dissemination. In our study, decanulation is still difficult to perform because patients have a low awareness to visit the doctor regularly. Sometimes, tracheotomy must to be maintained until adolescent or adult so the risk of obstruction become smaller.

Percentage of the aggressive disease is 82,4%. Some of aggressive RRPs found by Buchinsky[11] about 81%. This study results match with those results. The high incidents of those aggressive RRPs correlated with high occurrences of aggressive factors that were discussed previously. All of patients in this study categorized as juvenile type RRP, which is similar to Buchinsky[11] and Maloney[14].

Juvenile RRP tend to lead to aggressive disease caused by incompetent immune system to against the viral invasion, result in rapid cell growth and cell division. It will make the surgery more frequently performed. HPV-11 infection causes more stronger proliferative ability than HPV-6 which stimulate the disease course to be more aggressive.[15]

Some literature findings by Wiatrak[12] were reported 53,5% of HPV-6 patients, 39,7% of HPV-11 and 6,9% of both types. Buchinsky[11] found 60% of HPV-6 infection and 40% of HPV-11. This study result similar to Buchinsky findings which showed tendency of HPV-11 infection rather than HPV-6. Maloney[14] was report several children have coinfection with HPV type 6 and 11.

Buchinsky[11] was found 43 aggressive RRP samples with HPV-11 infection and 52 patients with HPV-6, while non aggressive RRP with HPV-6 infection were 19 patients and 4 patients with HPV-11. The result showed that HPV-11 tend to cause more aggressive compared to HPV-6 and that association was statistically significant with $p = 0,02$ ($p < 0,05$).

It shows not only HPV that cause the aggressiveness of the disease but also, other aggressive aspect is host factor, particularly immune response and host suscepbility. One patient might have more aggressiveness type while others have mild type. The host susceptibility against viral infection is related with polymorphism of immune response regulator gene. Effective immune responses against viral infection involve innate or adaptive immune response, Th1 and Th2 balances with certain chemokines and cytokines. This immune response can even control and predict the disease susceptibility and aggressiveness. We need more investigation to clarify the role of host respon to the HPV.[14,15]

There are several limitations on this study. First, we have a short of time to collecting samples and make small number of samples. Second, all patients are from one single center, perhaps multicenter national study more reliable.

CONCLUSION

This study presented that viral type of HPV have no association with aggressiveness of the disease and could not be used as a prognostic maker of the disease course. But the RRP patients need a regular follow up and proper treatment during the disease course, particularly for the aggressive disease.

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