Juvenile Recurrent Respiratory Papillomatosis

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An initiative of Otolaryngology online

Introduction

Predominant sites involved: Epithelial transition zone - where there is a change in epithelium from squamous to cilited columnar epithelium.

This is potentially life threatening disease characterized by development of papillomata anywhere in the respiratory tract from the nasal vestibules to the terminal bronchi.

Commonly seen in: Tonsillar pillars Uvula Vocal folds Laryngeal commissur e

This disease has bimodal distribution. Juvenile onset peak occur at 3-4 years Adult type peaks at 20-30 years of age

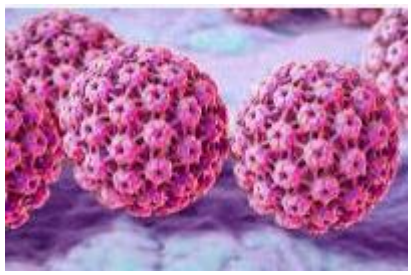
75% of juvenile papillomas are identified before the age of 5.

Papilloma of younger age group is a more aggressive disease and is known to affect multiple sites. Adult onset papillomas are usually solitary and are more common in men. It spreads via sexual contact or via indirect contact with anogenital lesions.

Aetiology

Caused by HPV types 6 and 11. HPV is a naked double stranded icosahedrally shaped virus with circular supercoiled DNA genome surrounded by an over capsid of protein that belongs to papovavirus family.

First described by Morrell Mackenzie in 1880
Ullmann in 1923 demonstrated the infective etiology by injecting homogenized papilloma from a child's larynx into his own forearm thereby inducing local growth of papilloma



Viral protein, DNA synthesis and virion assembly only takes place in the granular and cornified layers of the terminally differentiated epithelium.

HPV first enters traumatized epithelium and resides in the basal layer of the mucous membrane, where it replicates by a process known as episomal maintenance. This replication interferes with the normal process of cell maturation, causing epithelial proliferation and neovascularization. Sometimes the virus may lie dormant causing subclinical infection and can often be recovered from apparently normal tissue adjacent to papillomas.

Epidemiology

Prevalence rate - 4 in 100 000 children
Susceptibility triad - young mother, vaginal delivery and low maternal socioeconomic status is of limited predictive usefulness.

Latent HPV has been detected in cervical swab in nearly a quarter of women in child bearing age.

Epidemiology

Nearly 1 in 400 infant delivered to women with genital wart subsequently develop Juvenile papilloma

A prolonged delivery time (exceeding 10 hours) conferred twofold increased risk. Delivery by Caesarean section did not appear to reduce the risk.

Other factors responsible include:
Immunological
Genetic
Timing / length / volume of exposure to HPV

Clinical Features

Even though respiratory papillomas can arise in any respiratory mucosa, their initial presentation is usually in the larynx

Misdiagnosis:
Asthma
Laryngitis
Bronchitis

Chronic cough
Hoarseness of voice
Stridor
Choking attacks
Recurrent respiratory attacks

The diagnosis requires high degree of awareness on the part of the surgeon as the presenting symptoms can be highly variable

Diagnosis

Macroscopically papillomas can be pedunculated, or sessile, spread over the mucosal surface of the larynx. They can be grasped and removed using microlaryngeal instruments. Specimen is sent for HPE.

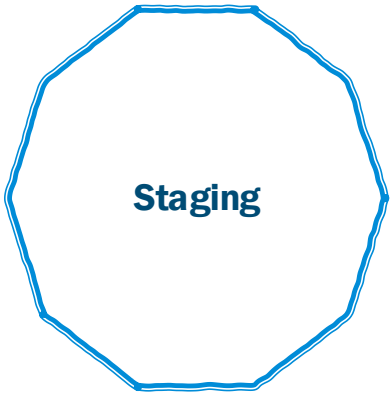
Prophylaxis against Laryngopharyngeal reflux is given before the actual surgery.

Awake fibreoptic bronchoscopy
GA is preferred in uncooperative patients.
The larynx is topically anesthetized with 2% xylocaine and anesthesia is manitained by sevoflurane and oxygen.

Microscopically, the papillomas appear as exophytic projections of keratinized squamous epithelium overlying a fibrovascular core with varying degrees of dyskeratosis, parakeratosis and dysplasia. Koilocytes (vacuolated cells with clear cytoplasmic inclusions)are often seen indicating viral infection.

Staging

Implementation of a staging system allows the practitioner to make an accurate comparison of the patient's disese between visits and to clearly communicate the disease severity with other physicians



Derkay staging

For each site, score as:
0 = none, 1 = surface lesion, 2 = raised lesion, 3 = bulky lesion

Larynx

Epiglottis:	Lingual surface ____
	Laryngeal surface ____
Aryepiglottic folds:	Right ____ left ____
False vocal folds:	Right ____ left ____
True vocal folds:	Right ____ left ____
Arytenoids:	Right ____ left ____
Anterior commissure	____
Posterior commissure	____
Subglottis	____

Trachea

Upper one third	____
Middle one third	____
Lower one third	____
Bronchi:	Right ____ left ____
Trachotomy stoma	____

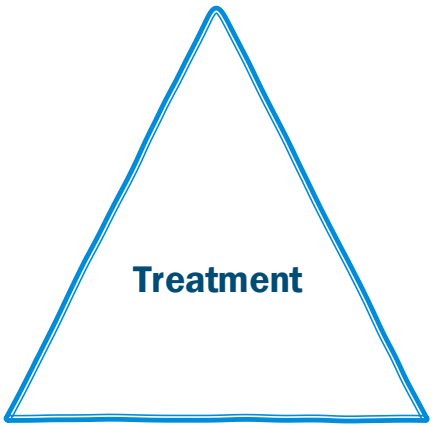
Other

Nose	____
Palate	____
Pharynx	____
Oesophagus	____
Lungs	____
Other	____

Total score all sites ____

Treatment

Aim of treatment is the removal of papillomas and restoration of a safe and patent airway while minimizing trauma to the mucosa and vocal cords.



Risk of scarring and webbing can be reduced by avoidance of two opposing raw surfaces, especially at the superior commissure. Papillomas do not extend beyond the basement membrane. Surgery can cause inadvertent damage to surrounding tissues.

Powered microdebrider:
Non serrated laryngeal blade is used with a setting of 300-700 rpm. This allows papillomas to be suctioned into the debrider with minimal cutting trauma to surrounding normal tissues. Laryngeal blade allows gentle and comprehensive removal off papillomas with minimum contamination of the lower respiratory tract with blood or papillomas. There is minimal damage to the mucosa.

Treatment (Contd)Cold steel surgery

Microlaryngeal instruments are used to remove papilloma using microflap technique. This minimizes trauma to the vocal fold while satisfying disease clearance. Thermal damage to neighbouring tissue is avoided. There is no vapour plume.

CO2, KTP, ND:YAG AND PULSED DYE-LASER:

Carbondioxide laser has been the main stay in the management of papilloma larynx for may years. Soft tissue complications can be minimized by appropriate laser settings and careful assessment of the depth of ablation. Two staged procedure can be performed in order to minimize damage to normal tissues without compromising complete tumor removal.

KTP laser and Nd:YAG laser are as effective as carbondioxide laser in papilloma ablation and hemostasis. The advantage of pulse dyed laser is that it can be fiber delivered and cause minimal vocal fold fibrosis with minimal vocal fold damage. But pulsed dye laser is not useful in removing large pedunculated tumors.

Photodynamic therapy:

This technique relies on the observation that rapidly proliferating tissue selectively takes up a number of photosensitizing agents when administered intravenously, and these agents release tumouricidal oxygen derivatives when activated by laser light of the appropriate wavelength.

Coblation:

This minimally invasive low heat technology that delivers a plasma layer to dissolve target tissue while maintaining the integrity of surrounding tissues. Special wands are designed to function at temperatures as low as 40-70 degrees Celsius.

Adjuvant Therapy

Antiviral therapies:
Drugs with antiproliferative / immunomodulatory properties.
Decision to implement adjuvant therapy must depend on careful consideration of the benefits against potential adverse effects of the therapy.

Interferon - Alpha:

These are produced naturally by human leucocytes. It has antiviral, antiproliferative and immunomodulatory properties. It exerts an indirect antiviral action by interfering with normal host cell translation mechanisms and by inducing synthesis of intracellular enzymes that act to control viral growth. It is administered systemically, by subcutaneous injection at a dose of 2-5 MU/m2 of body surface area.

It can cause pancytopenia, hepatorenal failure and cardiac dysfunction.

Bevacizumab:
(Avastin) is a recombinant monoclonal antibody that inhibits angiogenesis (VEGF - A). It has shown promise with systemic / intralesional administration. It is administered at a concentration of 2.5 mg/ml for three consecutive injections at 2-3 week intervals, and can be used in conjunction with cidofovir.

Cidofovir:
This is active against a broad spectrum of DNA viruses including CMV, EB virus and HPV. Its mechanism of action is by inhibition of viral DNA polymerases essential for viral replication.

Ribavirin:
Is active agains a broad spectrum of viruses. It is principally used as an aerosol in the treatment of RCV pneumonia. It can be used as aerosol or systemically.

Adjuvant therapy (Contd)

Acyclovir:
It has been suggested that the mechansim of action of acyclovir is to eradicate HSV.

Indol-3-Carbinol:
This is derived from cabbage / Broccoli. It affects oestrogen metabolism shifting production to antiproliferative oestrogen. This drug can be used as an adjuvant in the treatment of juvenile respiratory papillomatosis.

Cimetidine:
It was first used in the management of cutaneous warts. It has an immunomodulatory effect. It can be used as an adjuvant

Tracheostomy is performed in patients if there is stridor

HPV vaccine is on trial as an adjuvant.