Recurrent respiratory papillomatosis

Introduction

Recurrent respiratory papillomatosis (RRP):
- A disease of viral origin, associated with exophytic lesions of the aerodigestive tract
- Tend to recur and to spread throughout the entire respiratory tree
- Benign lesions, but can be fetal
  - airway obstruction, distal airway spread, and malignant transformation

- The course of RRP: variable
- Juvenile onset (JORRP): RRP diagnosed before 12 years of age
- Adult onset (AORRP)

Etiology

Human Papilloma Virus (HPV):
- A small, nonenveloped icosahedral (20-sided) capsid virus with double-stranded circular DNA
- At least 100 different types of HPV
- Associated with RRP: HPV types 6, 11, 16, 18
- The cause of RRP: the same viral subtypes associated with 80-90% of cases of genital warts (condyloma acuminata).
- Type 11: more virulent than type 6
- HPV targets epithelial cells exist within its host in an active or latent form
- Increase the level of expression of epidermal growth factor receptor and its ligands induce proliferation of epithelial cells
- Host immune system

Epidemiology

- Affect individuals of any age, from 1 day old to 84 years old
- A bimodal age distribution: peaks at 2-4 years and 20-40 years
- AORRP: men : women =3:2; JORRP: boys: girls=1:1
Incidence
- USA (4.3 per 100,000 children vs. 1.8 per 100,000 adults)
- Denmark (3.62 per 100,000 children vs. 3.94 per 100,000 adults)

Affected children undergo an average of 4.4 surgical procedures per year, or 19.7 procedures over their lifetime.
½ of affected adults undergo less than 5 procedures over a lifetime

JORRP
- The most common benign neoplasm of the larynx among children
- The second most frequent cause of hoarseness among children
- Typically diagnosed between 2 and 4 years of age
- 75% of children are diagnosed before age 5
- Children diagnosed at an earlier age tend to have more severe disease
- An average delay of 1 year before diagnosis
- 75% of children with RRP: first born
- Risk factor for JORRP: The triad of a first-born child, a vaginal delivery, and a teenage mother; low socioeconomic status

HPV in the lower genital tract
- Manifest as condylomata acuminata involving the cervix, vulva, or other anogenital sites in women
- Colposcopic (subclinical) changes: 5 million US women (3%)
- 10% of the at-risk population: DNA-positive but have no visible lesions
- 60% of the at-risk population: HPV antibody-positive but DNA-negative
- Clinically apparent HPV infection: 1.5% to 5% of pregnant women
- HPV 6, 11: the most common subtypes in cervical condylomata.

Transmission
JORRP
- The precise mode of disease transmission: unclear
- Active or prior genital HPV infection: 50% of mothers of affected children

Vertical transmission from mother to child
- Nasopharyngeal secretions of infants exposed to HPV in the birth canal: 30% with HPV
- The risk of a child contracting RRP following vaginal delivery from a mother with active genital lesions: 0.25 % (1/400)
- Associated factors: Patient immunity, timing, length, volume of virus exposure, local trauma

Hematogenous spread of HPV in utero
- Cesarean section to protect against RRP
  - 1 of 109 children delivered via Cesarean section to mothers with condyloma acuminata still developed RRP
Prophylactic Cesarean section: strongly considered in young, primiparous women with recently acquired HPV

Post-natal contact with an infected mother

AORRP

- associated with oral-genital contact
- Risk factors for AORRP: a large number of sex partners and frequent oral sex
- AORRP, JORRP, and condyloma acuminate
- the transmission of HPV disease: dose of the infecting agent, close and prolonged contact to HPV, and recipient susceptibility

Histology/Gross Appearance

- Gross
  - sessile or pedunculated masses, pink to white in color, in irregular exophytic clusters
- Histology
  - finger-like projections of nonkeratinized stratified squamous epithelium supported a core of highly vascularized connective tissue stroma

The basal layer: normal or hyperplastic; mitotic figures limited to this layer.

- Cellular differentiation: abnormal, with altered expression and production of keratins.
- The degree of atypia: a sign of premalignant tendency
- Malignant transformation of RRP into squamous cell carcinoma
- Most often occurs at a junction between ciliated epithelium and squamous epithelium
  - limen vestibuli, nasopharyngeal surface of the soft palate, midline laryngeal surface of the epiglottis, upper and lower margins of the ventricle, undersurface of the true vocal cords, carina, and bronchial spurs
- Common occurrence at tracheotomy sites (iatrogenic squamo-ciliary junctions).
- Trauma causes squamous metaplasia of respiratory epithelium
  - RRP flourishes in the setting of uncontrolled GERD

Clinical Presentation

- The most common presentation of RRP: hoarseness.
- The hallmark triad of JORRP
  - progressive hoarseness, stridor, and respiratory distress.
- chronic cough, paroxysms of choking, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, and acute life threatening events
- Adults: most commonly present with hoarseness, but may also present with globus pharyngeus.
- Stridor present since birth: laryngomalacia, subglottic stenosis, TVC paralysis, or a vascular ring, but RRP is still a possibility
- gradual and progressive onset of stridor and dysphonia over weeks to months: neoplastic growth such as RRP

**Physical examination**
- Child in respiratory distress
  - flaring of the nasal alae, use of accessory neck and chest muscles, cyanosis, and hyperextension of the neck
- Respiratory distress in children
  - transported immediately to the OR (preferable), ICU, or ER
  - establish a safe airway
- A flexible nasopharyngoscopy and laryngoscopy
- Endoscopy under anesthesia

**Staging**
- Established by University of Washington (Seattle) and licensed to the American Society of Pediatric Otolaryngology (ASPO),

<table>
<thead>
<tr>
<th>LARYNX</th>
<th>Clinical Score</th>
<th>Anatomical Score</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Describe the patient's voice today: normal (0), abnormal (1), aphonic (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Describe the patient's stridor today: absent (0), present with activity (1), present at rest (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Describe the urgency of today's intervention: scheduled (0), elective (1), urgent (2), emergent (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Describe today's level of respiratory distress: none (0), mild (1), moderate (2), severe (3), extreme (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Clinical Score (Questions 1 through 4) =</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. Clinical Score</td>
<td>B. Anatomical Score</td>
<td>C. Total Score = Total Anatomical Score plus Total Clinical Score</td>
</tr>
</tbody>
</table>
Surgical Treatment

Approach to surgery

- No therapeutic regimen that completely eradicates HPV from the airway
- The aims of therapy in extensive disease
  - to reduce the tumor burden
  - decrease the spread of disease
  - create a safe and patent airway
  - improve voice quality
  - increase the time interval between surgical procedures
- Latent virus remain in adjacent tissue after the removal of all clinically evident papilloma
- Remove as much disease as possible without causing subglottic and glottic stenosis, web formation, or diminished airway
- Remove gross disease with an endotracheal tube in place
- Extubation and apneic excision
- Jet ventilation
  - increased risk of distal airway spread, risk of pneumothorax, excessive mucosal drying, and gastric distention.

Carbon dioxide laser

- The most popular tool
- A wavelength of 10,600 nm vaporizes water and cauterizes tissue surfaces
- The smallest possible laser-safe endotracheal tube
- The cuff is used filled with saline rather than air to decrease the risk of an airway fire
- All members should wear micropore laser filtration masks and eye protection
- To use suction to minimize exposure of patient and staff to the laser plume
- Operative field draped with moist towels, and patient’s eyes protected with moist eye pads
- Cup forceps to obtain a specimen for surgical pathology from the site of bulkiest disease
- The laser should not be used until the oxygen concentration has decreased to 26-30%
- A avoid lasing both TVC’s in the area of the anterior commissure
- A rigid endoscope or a bronchoscope to examine the tracheobronchial airway
- The newest generation of laser microspot micromanipulator enables the surgeon to debulk papilloma initially in a defocused mode and then focus to a 250-nm spot size
- The KTP and argon laser: not as popular as the CO2 laser
- Common complications: scarring, webbing, and alteration of the mucosal wave
- Uncommon complications: airway stenosis, airway perforation, and airway fire

Microdebrider

- Now favored over the use of laser and cold steel microlaryngoscopy techniques
- Uses a small, protected oscillating blade coupled to suction
- Allows papillomas to be brought into the blade for shearing and removal.
- Used with a rigid endoscope, it is easy to remove subglottic and even tracheal lesions
A shorter operating time, less pain, and less expense than did patients treated with the laser
Less likely to cause laryngeal scarring than the CO2 laser.
Safer and more accurate than the laser and prevents thermal injury with minimal postoperative edema

**Cold steel excision**
- The lowest risk of scar formation in the true vocal folds
- Zeitels and Sataloff
  - no papilloma recurrence at 2 years of follow-up among 6 adults who underwent resection for primary disease
  - underwent surgery for recurrent papillomatosis, 6 of 16 (38%) continued to have recurrence after their microflap procedure
- The Voice Committee of the American Academy of Otolaryngology-Head and Neck Surgery pronounced in 2002
  - cold steel excision: the preferred technique for adults with RRP
- not burn tissue, nor does it result in a laser plume
- more bleeding than CO2 laser

**Revision Surgery**
- No surgical technique has consistently accomplished long-term eradication of RRP
- A mean lifetime number of procedures of 19.7 per child, with 4.4 procedures per year
- Children in whom RRP diagnosed before 3 years of age V.S. diagnosed after their fourth birthday
  - 3.6 times more likely to require more than 4 surgical procedures per year
  - 2.1 times more likely to have 2 or more anatomic sites involved
- The reoperation rate among adults
  - >75% of children required 5 or more procedures over their lifetime
  - only 50% of adults required the same frequency of surgery

**Tracheotomy**
- Up to 14% of children with JORRP require tracheotomy
- Should be avoided unless absolutely necessary
- To be decannulated as soon as the disease process is under adequate control
- Prolonged tracheotomy and subglottic papilloma present at the time of tracheotomy
  - an increased risk of distal tracheal spread.
  - ½ of tracheotomized patients: develop peristomal and/or tracheal lesions

**Progression**
- Extralaryngeal spread of RRP: 13% to 30% of children and 16% of adults
- Commonly involved sites in children: the oral cavity, trachea, and bronchi
- Commonly involved sites in adults: oral cavity and oropharynx
- Chronic invasive papillomatosis: malignant transformation (2-3% of cases)
- Death usually occurs secondary to a complication of frequent surgical procedures or respiratory failure from distal disease progression
Adjuvant Treatment methods

- 20% of patients: require adjuvant medical therapy
- The most common criteria for adjuvant treatment
  - More than 4 surgical procedures required per year
  - Distal multisite spread
  - Rapid regrowth of disease with airway compromise

Cidofovir

- A cytosine analogue with potent activity against Herpes viruses family by inhibiting viral DNA polymerase
- FDA approved for HIV positive patients with CMV retinitis
- Induce apoptosis in HPV-positive cells
- An intracellular half-life of up to 65 hours
- No adverse effects noted with intralesional use in either children or adults
- In one study in adults, 100% of subjects achieved remission with no visible papilloma after a mean of 6 injections at 1-month intervals without any surgical debulking
- The primary safety concern with cidofovir: possible tumorigenicity

Interferon

- The exact mechanism of action is unknown
- Block the viral replication of RNA and DNA
- Alter cell membranes less susceptible to viral penetration
- Side effects: common
  - Acute reactions include fever, flu-like symptoms, chills, headache, myalgia, anorexia, paraesthesia, and nausea.
  - Chronic reactions include neutropenia, decreased growth rate, elevated liver transaminases, spastic diplegia, febrile seizures, thrombocytopenia, rashes, dry skin, alopecia, pruritis, renal insufficiency, and fatigue.
  - Severity of these symptoms may be decreased by nighttime administration
- Dosing typically starts at 5 million Units/meter-squared QD X 28 days, then 3 days/week X 6 months given subcutaneously
- Complete resolution: in 30-50%, with partial resolution in 20-42%
- A recurrence rate of approximately 50%

Photodynamic therapy

- The transfer of energy to a photosensitive drug
- The administration of a photosensitizing medication (dihematoporphyrin, DHE)
- The argon pump dye laser is then used on the lesions
- A small but statistically significant decrease in growth of papillomas
- The downside: to become very light sensitive for a period of 2-8 weeks
- A relatively new drug, mtetra(hydroxyphenyl) chlorine (Foscan)

Indole-3-Carbinol (I3C)

- an FDA-approved dietary supplement
The mechanism of action involves estrogen metabolism, with a shift to production of antiproliferative estrogen

I3C may not maintain its effectiveness when taken with antacids or H2-blockers

Preliminary results have shown a complete response in 1/3 of patients, a partial response in 1/3 of patients, and no response in 1/3 of patients

**Ribavirin**

An antiviral drug used to treat respiratory syncytial virus pneumonia in infants

A small trial in 8 patients using ribavirin in an oral form at 23 mg/kg per day divided 4 times daily after an initial intravenous loading dose

- An increase in surgical interval

**Acyclovir**

Acts via thymidine kinase, an enzyme that is not produced by papillomavirus

HPV coinfection with HSV, CMV, and EBV

**Contributing medical conditions such as asthma and GERD should be controlled.**

**Vaccination**

A quadrivalent (HPV type 6, 11, 16, 18) vaccine is undergoing phase III clinical studies.

The preliminary results regarding the HPV 16/18 vaccine for prevention of cervical dysplasia in women of child-bearing age were very encouraging