The Clinical Spectrum of Herpesvirus Infections

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Objectives

• Recognize the herpesviruses that cause disease in humans
• Understand the clinical presentations of herpesvirus infections

Herpesviruses overview

• > 100 known herpesvirus
  • 8 human herpesviruses
• Greek word herpein – “to creep or crawl”
  • referring to the latent, recurring nature
• All herpesviruses can establish latent infection within specific tissues, characteristic for each virus

History of herpesviruses

Herpes infection described by Hippocrates
1954 – Varicella isolated in culture
1958 – Link between Burkitt’s lymphoma and infection first suggested
1986 – HHV-6 discovered in patients with lymphoproliferative disorders
1994 – HHV-8 identified in biopsies from Kaposi’s sarcoma
1875 – Varicella determined to be infectious
1956 – CMV discovered
1964 – EBV identified in patients with Burkitt’s
1990 – HHV-7 identified in healthy individual
**Herpesviridae Subfamilies**

**Alphaherpesvirinae**
- GS-1, HSV-2, VZV - Broad host range
- Rapid reproductive cycle,
- Cytopathic effect and spread in culture
- Latent infections: Neuronal (sensory ganglia)

**Betaherpesvirinae**
- HSV-1, HSV-2, VZV - Restricted host range
- Slow reproductive cycle
- Latent virus: Leukocytes (CD34+), Hematopoetic stem cells, and secretory glands (Salivary glands, and renal tubule).

**Gammaherpesvirinae**
- Most Restricted Host Range
- Replicate in lymphoblastoid Cells
- Viruses specific for B or T cells
- Latent or lytic infection

**Shared properties of human herpesviruses**
- Code for unique enzymes involved in the biosynthesis of viral nucleic acids
- Synthesis and assembly of viral DNA is initiated in the nucleus
- Release of progeny virus from the is accompanied by cell death
- Establish latent infection within tissues

**HHVs can cause severe and atypical disease in immunocompromised patients**

**Immunosuppression**
- Medications
- HIV
- Cancer/Transplant

**Host Barrier defects** (MUCOSITIS, Eczema, Burns)

**Immune defects**
- Neonates
- Pregnancy
- Elderly
- Cellular defects
Diagnosis of Herpesviruses

- Isolation virus through culture and/or detection of viral genes or gene products
- Direct visualization
- Serology
- Polymerase chain reaction

Case #1

- A 4 year old F presents to your office with a swollen, painful, right index finger. You notice multiple fluid-filled lesions on the finger, as well as some small ulcers on her tongue and bleeding around her gums. What’s the diagnosis?

Image courtesy of Dwight Powell

HSV - Pathogenesis

Primary infection: high titer and prolonged infection

Establish Latency: provide reservoir and viral template for future secondary infections

Secondary Reactivation: lower titer and shorter duration but there are some who have more prolonged disease

Clinical Manifestations of HSV

Modified from image SC # 13
Tonye A. Ogele OpenStax CNX
Download for free at http://cnx.org/contents/1a4a3bd1-f368-4827-985e-7fcfe1bac6ef@1
Diseases Caused by HSV: Oral & Cutaneous

Images courtesy of Dwight Powell

HSV Gingivostomatitis in Immunocompromised

Images courtesy of Dwight Powell

Percent of U.S. population positive for herpes viruses: 2005-2010

Bradley et al, JID 2013
An unimmunized, previously healthy 25-year-old woman presents to your office with a 24-hour history of fever, malaise, and a generalized pruritic rash. Physical examination reveals a temperature of 38.6°C, respiratory rate of 25 breaths/min, heart rate of 88 beats/min, and blood pressure of 110/62 mm Hg. She has a papulovesicular rash over her face, trunk, and extremities that involves her scalp but spares her palms and soles. The remainder of her exam is normal. What is your diagnosis?
Varicella-Zoster Virus (VZV)
Pathogenesis Primary infection

- **Entry**: Respiratory route
  - Local replication
- **Primary viremia**: seeds liver/spleen
  - T cells and Antibodies limit primary viremia in people with prior immunity
- **Secondary replication cycle**
  - Amplification Liver and Spleen
  - Secondary viremia hematogenous dissemination to cutaneous sites.
- **Immunity**: T-cell response and resolution of lesions, IgG present
- **Virus establishes latent virus in dorsal root ganglia**

Varicella-Zoster Virus

- **Transmission**: direct contact or aerosol
- **Incubation**
  - Mean 14-16 days (10-21 days)
  - Contagious 1-2 days before rash and until lesions crusted
- **Increased severity**
  - Immune compromised
  - Older age
  - Pregnancy
- **250-500 lesions wild-type infection; in immunized, ≤ 50 lesions**

Herpes Zoster

GABHS periorbital cellulitis and necrotizing fasciitis complicating varicella
Necrotizing Fasciitis


Case #3

- A 1 day old male is born to a mother with no significant prenatal history. Delivery is uncomplicated but initial examination reveals hepatosplenomegaly and a “blueberry muffin” rash. Labs show thrombocytopenia and elevated liver enzymes. What's your diagnosis?
Cytomegalovirus Clinical Syndromes

- Congenital infection
- Mononucleosis syndrome
- Immunocompromised hosts: may develop life-threatening disseminated disease

CMV Seroprevalence

<table>
<thead>
<tr>
<th>Age</th>
<th>Seroprevalence</th>
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<tbody>
<tr>
<td>6-11 y</td>
<td></td>
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<tr>
<td>12-19 y</td>
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<tr>
<td>20-29 y</td>
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<tr>
<td>30-39 y</td>
<td></td>
</tr>
<tr>
<td>40-49 y</td>
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Congenital CMV

- Hepatosplenomegaly
- Retinitis
- Rash
- Central nervous system involvement

- Leading nongenetic cause of sensorineural hearing loss in US
  - Up to 50% of symptomatic infants
  - Up to 15% of asymptomatic infants

CMV Clinical Manifestations

- 90% asymptomatic
- Mononucleosis syndrome (20-50% cases)
  - Fever - most prominent
  - Increased SGOT/SGPT (90%)
  - Rash, particularly following ampicillin (EBV>CMV)
  - Atypical lymphocytosis
  - Exudative pharyngitis (EBV >> CMV)
  - Hepatosplenomegaly (EBV > CMV)
  - Adenopathy (EBV > CMV)
  - Aseptic meningitis, encephalitis, G B Syndrome
CMV – Immunocompromised Hosts

- Arthralgia
- Leukopenia
- Pneumonitis
- Retinitis
- Enterocolitis
- Polyradiculopathy
- Deterioration of graft function

Case #4

- A 15yo male presents to your office with fever, sore throat, and swollen glands in the neck. Exam reveals exudative pharyngitis, bilateral cervical adenopathy, and milar hepatosplenomegaly. What's your diagnosis?

Epstein-Barr Virus

- Present in human populations from all part of the world
- Acquisition occurs at an earlier age in underdeveloped countries
  - Adolescent seroprevalence:
    - Undeveloped: >90%
    - Developed: 40-50%

EBV

Clinical Manifestations - Acute

- Asymptomatic (frequency inversely related to age)
- Mononucleosis syndrome
- Neurologic/Neuropsychiatric
  - Nerve palsy, esp. Bell’s palsy
  - Guillain-Barré Syndrome
  - Aseptic meningencephalitis
  - Transverse myelitis
  - "Alice-in-Wonderland" Syndrome
- Thrombocytopenia/purpura
EBV Mononucleosis Syndrome

- Fever
- Lymphadenopathy
- Pharyngitis
- Splenomegaly
- Hepatitis
- Skin rash
- Pneumonitis
- Neurologic
- Myocarditis/pericarditis
- Thrombocytopenia
- Anemia
- Granulocytopenia

EBV Complications

- Splenic rupture
- Airway obstruction
- Fulminant hepatitis
- Myopericarditis
- Meningoencephalitis
- Thrombocytopenia
- Hemolytic anemia
- Orchitis

EBV in Immunocompromised Hosts

- X-linked lymphoproliferative syndrome
- Post-transplant B cell lymphoproliferative disorders
- HIV-associated B cell lymphoma
- HIV-associated oral “hairy” leukoplakia
- HIV-associated LIP
- HIV-associated leiomyosarcoma
**EBV-associated malignancies**

- Burkitt lymphoma
- Nasopharyngeal carcinoma
- Hodgkin’s disease (some are EBV-associated)
- HIV-associated
  - B cell, non-Hodgkin lymphoma
  - Smooth muscle (leiomyoma, and leiomyosarcoma)
- Lymphoma

**EBV Seroprevalence**

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-Hispanic Black</th>
<th>Non-Hispanic White</th>
<th>Mexican-American</th>
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<tbody>
<tr>
<td>6-8 y</td>
<td></td>
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<td>9-11 y</td>
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<td>12-14 y</td>
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<td>15-17 y</td>
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<tr>
<td>18-19 y</td>
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</tbody>
</table>

**Diagnosis of EBV**

- Direct visualization
- Serology
- Polymerase chain reaction

*Courtesy of Red Book Online.® 2009*
Case #5

A 13-month-old female developed high fever that persisted for 4 days without recognized cause. The child appeared relatively well and the fever subsided to be followed by a maculopapular rash that began on the trunk and spread to involve the face and extremities. What’s your diagnosis?

Human Herpesvirus 6 & 7

Human herpes viruses 6 and 7 are associated with exanthem subitem (roseola) and rejection of transplanted kidneys.

- Antibodies to this HHV-6 present in almost everyone by age 5.
- HHV-7 ubiquitous: >95% of adults seropositive.
- HHV-6 can also be recovered in vivo from a broad range of tissues.

HHV-6 Clinical Manifestations

- High fever
- Irritability
- Adenopathy (cervical and occipital)
- Maculopapular rash
- Inflamed tympanic membranes
- URI symptoms
- GI symptoms: vomiting and diarrhea
- Bulging anterior fontanelle
- Febrile seizures (15%)

HHV-6 Less Common Manifestations

- Arthritis
- Hepatitis
- Heterophile - negative mononucleosis (primarily adults)
- Intussuscepton
- Thrombocytopenia
- Neurologic (aseptic meningitis, meningoencephalitis, multiple sclerosis)
- Syndromes in immunocompromised patients
  - Suppression of marrow in BMT
  - Interstitial pneumonitis in BMT/HIV
  - Organ dysfunction/graft rejection
  - Skin rash
HHV-7 Clinical Manifestations

- Fever
- Maculopapular rash
- Irritability
- Lymphadenopathy
- Mild diarrhea
- Hepatitis

Case #6

• A 34 year old HIV+ male presents to your office with complaints of a lump in his mouth. He has been noncompliant with medications, his viral load is >2 million copies/ml and his CD4 lymphocyte count is 143 cells/mm³. Exam reveals a firm, fleshy lump on the hard palate.

- What's your presumptive diagnosis?

Human Herpesvirus 8

- Kaposi's sarcoma-associated herpesvirus (KSHV)
- Manifestations of 1° infection not well characterized
- HHV-8 is implicated as the etiologic agent of:
  - Kaposi's sarcoma (HIV+/HIV-) (found in 95%)
  - Monoclonal B cell lymphomas in HIV
  - Multicentric Castleman's disease

HHV-8 Epidemiology

<table>
<thead>
<tr>
<th>Population</th>
<th>Seropositivity Rate</th>
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<tbody>
<tr>
<td>US Children</td>
<td>2 - 8%</td>
</tr>
<tr>
<td>US adults</td>
<td>25%</td>
</tr>
<tr>
<td>US HIV+ IVDU</td>
<td>23%</td>
</tr>
<tr>
<td>US HIV+ women</td>
<td>21%</td>
</tr>
<tr>
<td>US HIV+ homosexual men</td>
<td>90%</td>
</tr>
<tr>
<td>US HIV+/KS+</td>
<td>96%</td>
</tr>
<tr>
<td>African endemic KS</td>
<td>100%</td>
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The take-home message…

Love May Not Last But Herpes Is Forever