Alphaherpesvirinae

Simplexvirus (HHV1&2/ HSV1&2)
Varicellovirus (HHV3/VZV)
HERPES SIMPLEX VIRUS

- First human herpesvirus discovered (1922)
- Two serotypes recognised – HSV-1 & HSV-2 (1962)
- HSV polymorphism occurs between strains
• HSV infects only humans and chimps and is distributed world-wide in all socioeconomic groups

• HSV-1 infection occurs early in life (by 15 years), and 40-60% of adults have been infected

• HSV-2 infections most prevalent in sexually active hosts, with prevalence rates of 7% at 15, to 25% in adults

• Transmission through close personal contact

• One third of the world’s population has recurrent HSV infections
Pathological changes induced are similar in both primary and reactivated infections.

Primary infections are generally more cytopathic.

Pathology involves virus-mediated cellular death and an associated inflammatory response.

In CNS infections oligodendritic involvement, gliosis and astrocytosis develop.
PATHOGENESIS

- HSV-1 infection is generally limited to the oropharynx. Transmission through respiratory droplets
- HSV-2 infection is usually acquired by sexual transmission
- Virus must come in contact with mucosal membranes or abraded skin for initiation of infection
- After primary infection virus is transported to dorsal root ganglia and remains latent
PATHOGENESIS

- Disseminated CNS infections may occur but are rare
- Occasionally primary infection results in systemic infection.
  (eg HSV infections with multiorgan involvement in neonates, during pregnancy and in the immunocompromised)
- Antibodies to one type do not protect from primary infection with the second type
HOST RESPONSE TO INFECTION

- HSV infections induces a humoral and cell-mediated host response
- IgM and IgG is usually produced during primary infections and cytotoxic T cells are evident
- Production of IgM is often absent in recurrent infections and suggestion that cytotoxic T cells are depressed
- In newborns, infection may occur even in the presence of maternal antibodies - suggests cell-mediated response is most important

In newborns cell-mediated immunity is not fully developed therefore often results in severe disease.
Primary Infection (HSV-1)

- Primary HSV-1 infections usually occur in young children and are most often asymptomatic.
- Manifestation of infection may include fever, sore throat, ulcerative and vesicular lesions, gingivostomatitis, oedema and lymphadenopathy.
- Incubation period of 2-12 days, and symptoms last for 2-3 weeks.
- Primary infection in adults often results in pharyngitis in association with mononucleosis syndrome.
**Latent Infection**

1. Asymptomatic - No virus or virion proteins produced

2. Viral DNA resides in sensory cells of Trigeminal nerve ganglion

**Recurrent Infection**

1. Virus replicates and travels down sensory nerve fiber to infect epithelial cells around the nose and mouth

2. Symptoms are usually a milder form of primary infection
Recurrent orpharyngeal infections occur in about 38% of the population.

Prodrone of pain, burning, tingling, followed by vesicles 24-48 hrs later (sometimes fever).

Recurrence may be asymptomatic. About 1-5% of healthy adults excrete HSV-1, 30% of immunocompromised.

Factors leading to recurrence are highly variable and poorly defined.
Genital herpes infection (usually HSV-2)

- Primary infections usually acquired through sexual contact
- Manifestation includes formation of macules followed by vesicles and postules and ulcers.
- Duration of 3 weeks. Virus is shed for about 19 days
- Most common complications are extragenital lesions (20%) and aseptic meningitis (10%)
Recurrent Herpes Genitalis

• Recurrent HSV-2 infection is generally milder, and complications are rare.
• The rule is that - more severe primary infection results in more severe recurrent episodes
• 1/3rd of infected individuals have 2-3 recurrences per year
• 1/3rd have 4-7 recurrences
• 1/3rd >8 (some may be almost continuous)
Keratoconjunctivitis

- 300,000 per year in USA
- Leading cause of blindness other than trauma
- unilateral or bilateral conjunctivitis
- photophobia, tearing, corneal ulcers, eyelid edema
- recurrence common usually unilateral and can last weeks or months
- progressive disease leads to visual loss even rupture
Herpes skin infections

- Localised or disseminated
- herpes gladiatorum
  - sumo wrestlers
  - rugby players
- herpes whitlow 2.4/100K
- mucocutaneous disease in immunocompromised
Herpes Encephalitis

- Sporadic fatal encephalitis, fever, altered consciousness, bizarre behaviour
- Localised temporal lobe disease
- >70% mortality if untreated
- Only 2.5% return to normal neurologic function
Neonatal herpes infections

- 1 in every 10,000 live births, infected through the birth canal
- Greatest risk in term mothers experiencing primary infection
- Majority asymptomatic, but symptoms may include vesicular disease, respiratory distress, hypoglycemia
- Skin vesicle in 70% of infected infants
- Leads to progression from isolated vesicles to involvement at other sites
- 75% of untreated babies die
- Vidarabine treatment reduces mortality from 75% to 38%
Diagnosis

• Experienced clinician can diagnose labialis and genitalis in 90% of cases

• Virus isolation and PCR the definitive diagnostic method. Need swabs containing cells from the base of the lesion

• Direct fluorescent antibody staining is a suitable alternative, especially if combined with virus isolation

• Presence of IgM and a rise in IgG are positive clinical indicators during primary infection, but are not useful in reactivation

• PCR shows potential for rapid diagnosis especially in CNS disease. However detects latent genome as well as infectious virus.
VARICELLA ZOSTER VIRUS

Varicella - Chicken Pox

Herpes Zoster
VARICELLA ZOSTER VIRUS

Varicella - Chicken Pox
Herpes Zoster
World-wide distribution and endemic in many larger cities

170,000 cases/yr reported in USA represents only 6% (4 mill estimated)

Highest incidence of varicella in 5-9 year olds with peaks of infection during winter & spring

The virus is very virulent with attack rates among exposed susceptible = 60-70%

97.5% of adults in US are seropositive (ie infected)

Clinical disease recognised in two forms

Primary infection - Varicella (Chicken Pox)

Reactivation - Zoster
PRIMARY VARICELLA PATHOLOGY

- Clinical disease is usually benign. Manifests as a viral exanthem
- Virus enters via mucosa of URT and oropharynx or via conjunctiva
- Viral replication occurs in primary site and virus disseminates via the blood stream.
- Virus replication then occurs in cells of the reticuloendothelial system (blood mononuclear cells)
- Virus replication is initially limited by specific and non-specific immunological responses but in most individuals these are overwhelmed and extensive secondary viremia occurs
Secondary viremia is associated with prodromal symptoms followed by cutaneous and mucosal lesions.

Viremia is usually terminated after 3 days by humoral and cell-mediated factors.

Prodromic symptoms first appear 14-15 days post-infection involving fever and rash.

Eruption into maculopapular rash forming lesions over 2-4 days. May appear on scalp, trunk, extremities and mucosal surfaces.

Vesicles dry over 1-3 weeks. Infectious virus found in vesicular fluid.
• Rises in titres of IgM, IgG and IgA are demonstrated within 5 days after the onset of symptoms

• Serious complication of primary infection (varicella) is pneumonia especially in neonates and immunocompromised.

• No evidence of congenital VZV infection

• Infections in the IC may involve lungs, liver and CNS and often is fatal

• CNS infection occurs most often in children between 4 and 15 years resulting in encephalitis.
SECONDARY ZOSTER PATHOLOGY

- Virus spreads to the ganglia by systemic virus
- Sets up latent infection in ganglion without replication or cell damage.
- Reactivation as herpes zoster involves the ganglia and spinal nerves corresponding to the dermatome involved in the primary infection
SECONDARY ZOSTER PATHOLOGY

• Reactivation is sporadic and infrequent and involves endogenous (immune) factors. Most frequent in immunosuppressed.

• Appearance of herpes zoster rash is preceded by 3 – 4 days of severe pain, followed by lymphadenopathy, headache, fever & malaise (sometimes motor paralysis)

• Eruption lasts up to 16 days. Continued vesiculation may result in lesions persisting for months

• The areas supplied by the trigeminal nerve (opthalmic) and thoracic ganglia are most often involved
VARICELLA ZOSTER DIAGNOSIS

• Diagnosis of primary VZV infection is often made on clinical presentation

• Resembles other rashes in infants and >10% misdiagnosis has been suggested

• Virus isolation provides a definitive diagnosis, although direct fluorescent detection of virus in cells scraped directly from vesicles is very efficient.
VARICELLA ZOSTER DIAGNOSIS

- Virus can only be detected in fresh lesions, up to 3 days in varicella, 7 days in HZ

- Detection of IgM, IgG and IgA is efficient in varicella but not useful for diagnosis of HZ

- PCR of cells from lesions and CSF is most sensitive and specific.