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

EPIDEMIOLOGY

- 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

PATHOLOGY

- 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 abraided 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

- Occassionally 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

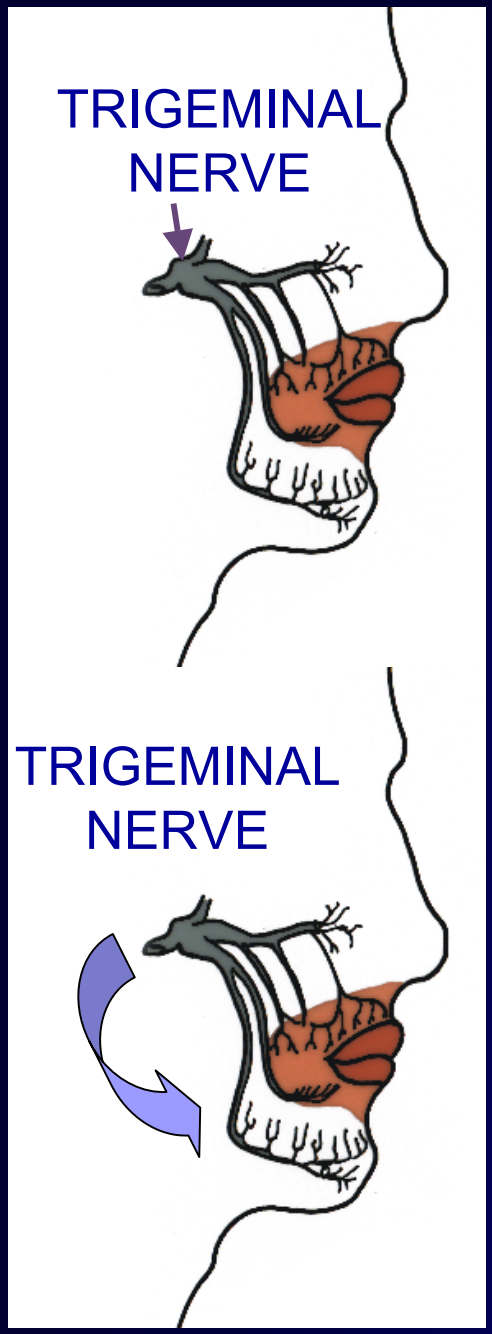
- HSV infections induces a humoral and cell-mediated host response
- IgM and IgG is usually produced during primary infections and cytotoxic T cells are evident
- Production of IgM is often absent in recurrent infections and suggestion that cytotoxic T cells are depressed
- In newborns, infection may 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.

CLINICAL MANIFESTATIONS OF HSV INFECTION

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

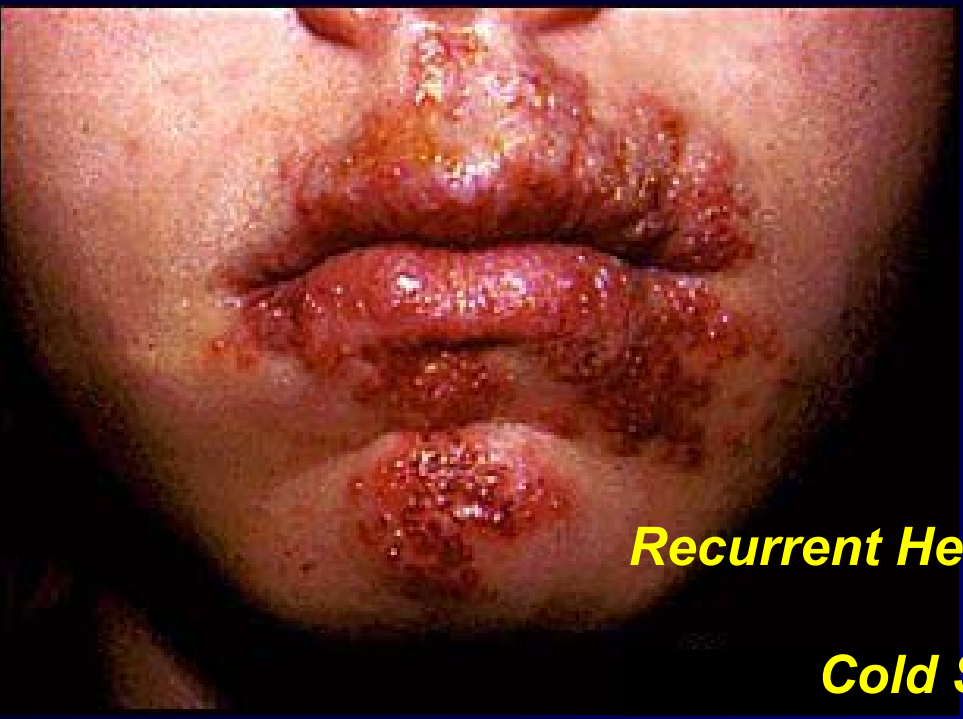
1. **Asymptomatic - No virus or virion proteins produced**

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 Herpes Labialis

Cold Sores

- **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

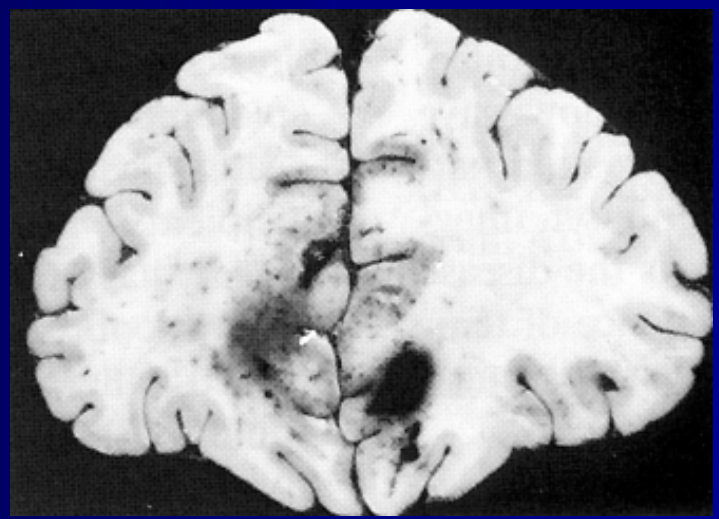
- 300,000 per year in USA
- Leading cause of blindness other than trauma
- unilateral or bilateral conjunctivitis
- photopobia, tearing, corneal ulcers, eyelid edema
- recurrence common usually unilateral and can last weeks or months
- progressive disease leads to visual loss even rupture

Herpes skin infections

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

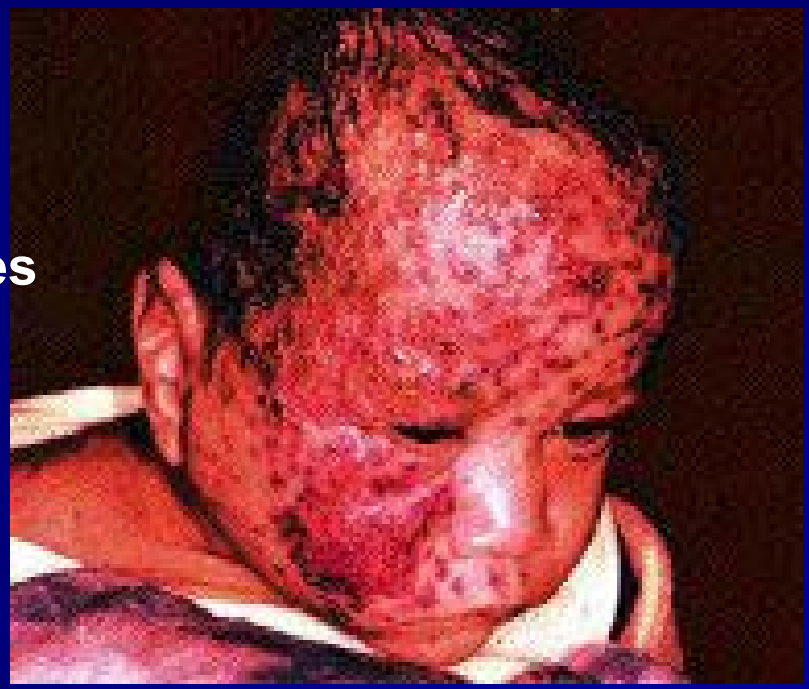
Herpes Encephalitis

- Sporadic fatal encephalitis, fever, altered consciousness, bizarre behaviour
- Localised temporal lobe disease
- >70% mortality if untreated
- 0nly 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

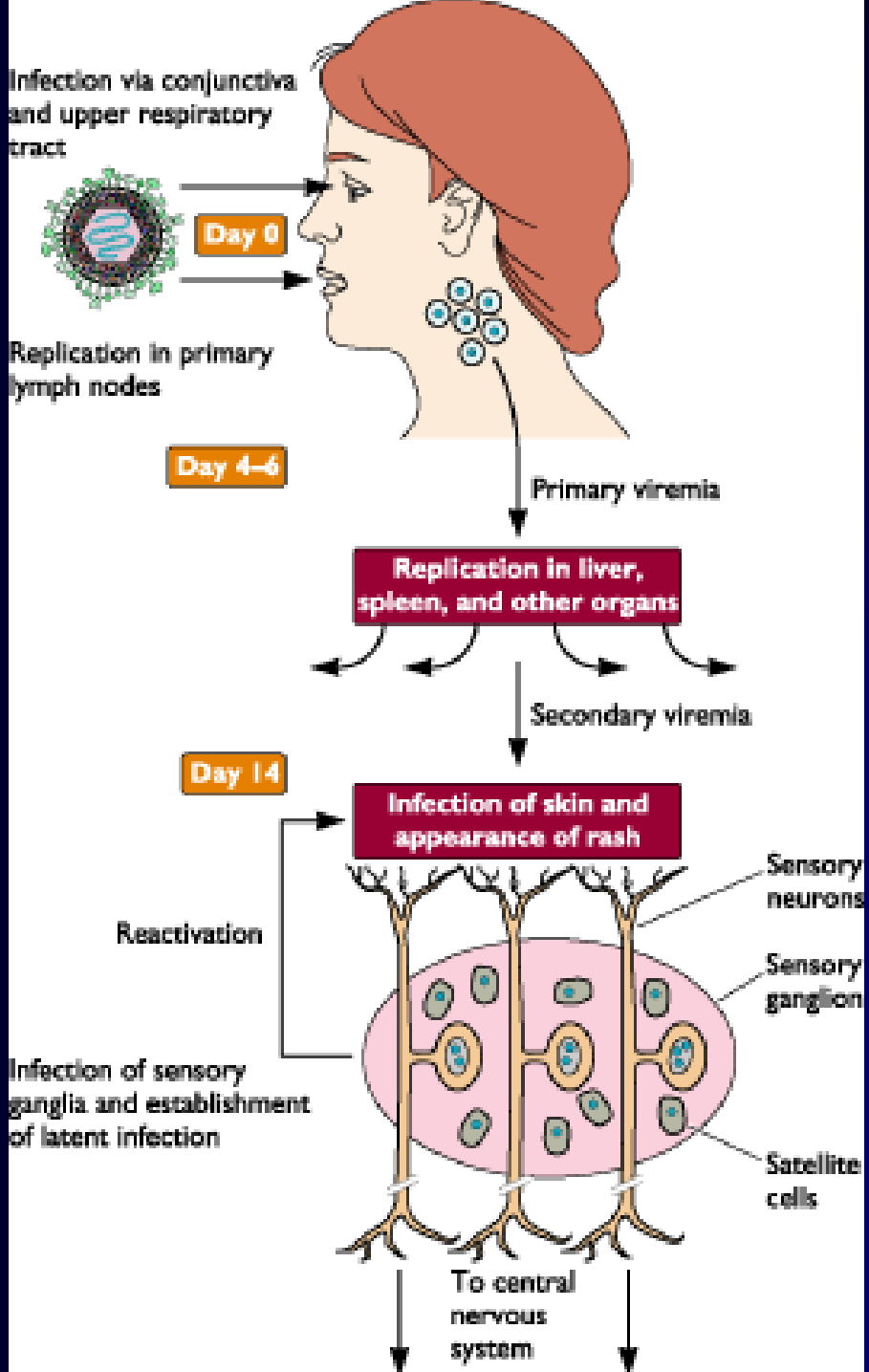
- World-wide distribution and endemic in many larger cities
- 170,000 cases/yr reported in USA represents only 6% (4 mill estimated)
- Highest incidence of varicella in 5-9 year olds with peaks of infection during winter & spring
- The virus is very virulent with attack rates among exposed susceptible = 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



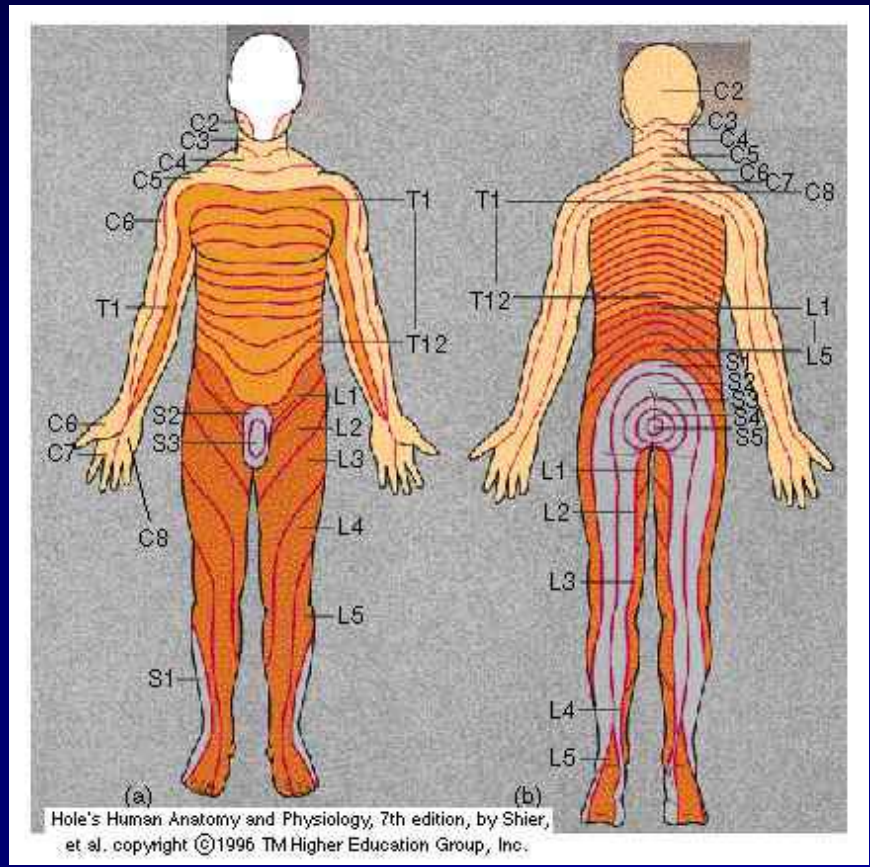
- Secondary viremia is associated with prodromal symptoms followed by cutaneous and mucosal lesions
- Viremia is usually terminated after 3 days by humoral and cell-mediated factors
- Prodromic symptoms first appear 14-15 days post-infection involving fever and rash
- Eruption into maculopapular rash 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.

PRIMARY VARICELLA CLINICAL

- 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.