Pathogenesis of viral infections

Pathogenesis: Refers to the interaction of viral and host factors that lead to a disease production.

Pathogenic virus: Virus that can enter to the host, produced virus-host cell interaction, causing the sign and symptoms of a disease.

Virulent strain: pathogenic virus that produce more severe disease.

Steps in viral pathogenesis:
1- Viral entry & Mode of transmission
2- Primary viral replication
3- Viral spread
4- Cellular injury
5- Cell & tissue tropisms
6- Host immune response
7- Viral clearance & establishment of persistent infection
8- Viral shedding

Cycle of infection

Entry → Primary site → Spread → Secondary sites → Shedding → Local Lymphatic Neuronal Blood (viremia) → Shedding
La-Viral entry: through the following systems:

- Respiratory Tract
- Gastrointestinal Tract

most common routes of viral entry

- Skin
- Urogenital Tract
- Conjunctiva

- blood born: by needles, insect vectors, blood Transfusion

**Routes of entry and shedding**

![Diagram of routes of entry and shedding](image)

Portals of entry of viruses into the host, and sites of shedding from the host. (From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Figure 9-2)

b- Mode of transmission:

- **Horizontal:** person-to-person (infl.v., herpes v., HIV)

- **Vertical:** from mother to offspring (rubella, HIV, CMV, Hepatitis B & C, parvo B19)

- **Zoonotic:** from animal to man (rabies v.)

- **No transmission:** due to reactivation of a latent, non-replicating virus can occurs within the individual infection (HSV1, HSV2 & CMV)
2-viral replication:

Localized infection: virus replicate at primary site locally as: influenza v. & rota v.) these viruses spread locally over the epithelial surfaces, and there is no necessity for further systemic spread, no invasion to under lying tissues nor spread to distant site.

Disseminated infection: viruses that produce systemic manifestation distant from the site of entry as: polio v. & Measles v

Features of acute viral diseases

<table>
<thead>
<tr>
<th>* Example</th>
<th>Local infection</th>
<th>Systemic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhino v.</td>
<td></td>
<td>Measles v.</td>
</tr>
</tbody>
</table>

* Site of

Pathology  portal of entry distant

* I.P  short long

* Viremia  - +

* Role of secretary

* IgA Ab in resistance  important not

* Duration of immunity variable-may be short life long

3-Viral spread Mechanisms:

Most common mechanisms for viral spread are through blood and Lymphatic

Neuronal spread (as: rabies v. and herpes v.) to ganglia to initiate latent infection.

Some virions are free in plasma …entero v. & toga v.

Or are associated with Particular types of cell (measles v.) and some viruses even multiply within these cells.

4-Cell tropism: virus tends to exhibit Organ &cell specificities and usually this tropism reflects:

1-The presence of specific cell surface receptors with viral surface (capsid or envelope) that can specifically interact &initiate infection.

2- Factors affecting viral gene expression; enhancer regions that show some cell type specificity may regulate transcription of viral genes. (e.g. JC a papova virus is more active in glial cell).

3- Proteolytic enzymes; certain paramyxoviruses are not infectious until an envelope glycoproteins undergoes proteolytic cleavage.
4- Specific viral genes; e.g. reoviruses, the extent of viral spread from GIT is determined by one of the outer capsid proteins.

5- **Cell injury & clinical illness:**

- **No apparent** morphological or functional changes

- **Cytopathic effect (CEP):**

  a- **Changes** in the cell appearance: Rounding, darkening and ballooning of cells.

  b- **Multinucleated Giant cells:** Due to fusion of virus infected cell as a result of cell membrane changes which caused by the insertion of viral proteins into the cell membrane (herpes v. & paramyxo v.)

  c- **Inclusion bodies:** discrete areas on cell cytoplasm or nucleus, containing viral proteins or viral particles e.g. Negri bodies (intracytoplasmic) by rabies v. and Owl’s eye inclusion (intranuclear) by CMV.

- **Malignant transformation:** uncontrolled cell growth & prolonged survival (oncogenic v.)

- **Cell Death:** due to inhibition of macromolecular synthesis either by inhibition of host cell protein synthesis or inhibition of DNA and RNA synthesis.

Some tissue regenerates rapidly like gastrointestinal epithelium and skin, whereas brain can’t.

- **Non lethal physiological alteration:** leads to impairment of specialized functions of cells such as a loss of hormone production.

**Clinical illnesses**

I.P: usually asymptomatic

**Prodromal period:** associated with non-specific symptoms

**Specific illness period:** characterized by signs & symptoms of the disease.

**Recovery period:** illness wanes & patient regains good health.

6- **Immunopathogenesis**

**Direct effect:** cell killing e.g. infection with *polio v.* (kill motor neuron cells leading to paralysis of the muscles)

**Ebola v.** causing hemorrhage due to the damage in vascular endothelial cells which caused by enveloped gp of the virus

**Indirect effect:** (immunological attack)

1- Cytokines produced by rotavirus-infected enterocytes that stimulate the enteric neurons resulting in excess fluid and electrolytes secretion into the bowel lumen.....causing diarrhea
2-cytotoxic T-cell are involved in the pathogenesis of hepatitis A, B & C not causing CPE, damage is due to recognition of viral Ag by cytotoxic T-cell.

Measles v. produce rash, cytotoxic T cell attacks infected vascular endothelial cell of skin.

3-Immune- mediated pathogenesis (virus-antibody complement complex) deposited in various tissues e.g. (HBV, Parvo B19; causing arthritis), and (RSV) causing pneumonia in infant due to maternal IgG-viral Ags complex.

Evasion of host defenses

1-Cytokine decoys: viral proteins block host immune mediators (IL1 /TNF)

2-reduce the expression of class I MHC proteins (HIV/Cytomegalovirus)

3-Inhibit complement (Herpes Simplex Virus).

4-Virokines: some viruses synthesized RNAs that block phosphorylation of initiation factor (elf-2), so that they reduce the ability of interferon to block viral protein replication. (HIV/ Epstein Barr/ adeno v.)

5- Multiple antigenic types; viruses with multiple serotypes (rhino v. more than 100 serotypes

Hepatitis C Virus: more than 6 serotypes.

7-Persistent viral infection:

Some time, the virus persists for long periods either intact or in the form of a subviral component (genome).

Mechanisms of Persistence:

1- Integration of a DNA provirus into host cell DNA e.g.: retroviruses

2- Immune tolerance: no NA

3-Virus –antibody complexes formation: which remain infectious

4- Location in an immunologically sheltered organ e.g. brain

5- Rapid antigenic variations

6- Spread from cell to cell without extra cellular phase.

7- Immunosupression (e.g. AIDS)
Types of Persistent viral infection:

-Chronic carrier: are those in which replicating virus can be continuously detected, often at low levels; mild or no clinical symptoms may be evident (the viral shedding continue for long period (as in chronic HBV or HCV or neonatal rubella &CMV)

-Latent infections: the virus persists in an occult (hidden or cryptic) form most of the time when no new virus is produced. There will be intermittent flare-ups of clinical disease; infectious virus can be recovered during flare-ups.

E.g. HSV; this virus enters a latent state in the cell of sensory ganglia once it's activated by a stress factors, recurrence of infection will occur.

Patterns of disease

From Schaechter’s Mechanisms of Microbial Disease; 4th ed.; Engleberg, DiRita & Dermody; Lippincott, Williams & Wilkins; 2007; Fig. 31-9
-Slow virus infections

Prolonged I.P & the progression of disease

Virus has a normal growth cycle, but not slow growth

Types of Slow virus infections

Conventional: * subacute seclerosing pan encephalitis (SSPE) which follows several years after measles v. infection.

**progressive multifocal leukoencephalopathy(PML), which caused by JC-virus, a papova v., disease occurs primary in patient who have lymphomas or immune compromised patients.

Non-Conventional: prions

(Non-Conventional viruses that causing (transmissible spongioform encephalpathies

In human:

Creutzfelds-Jacob disease

Kuru

In animal:

Mad -cow disease

Scrapie -sheep

Prions are Infectious particles that are composed solely of protein, no detectable nucleic acid

E/M: revealed filaments.

It's very resistant to U/V, heat, formaldehyde, nuclease but can be only inactivated by hypochlorite, sodium hydroxide and autoclave.

Features

<table>
<thead>
<tr>
<th>prions</th>
<th>conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>-particle containing nucleic acid</td>
<td>no</td>
</tr>
<tr>
<td>-particle containing protein</td>
<td>Encoded by cellular gene</td>
</tr>
<tr>
<td>-inactivated by U/v</td>
<td>no</td>
</tr>
<tr>
<td>or heat</td>
<td></td>
</tr>
<tr>
<td>-E/M appearance</td>
<td>filamentous(amyliod)</td>
</tr>
<tr>
<td>-Ab production</td>
<td>no</td>
</tr>
<tr>
<td>-Induce inflammation</td>
<td>no</td>
</tr>
</tbody>
</table>
8-Viral shedding:

Last stage that Maintain viral infection in population or in the environment.

Shedding occurs from body surface which involved in viral entry. Patient remains infectious to contacts.

Dead-end infection in human occurs only in Rabies, Poliomyelitis and SSPE in these cases there are no viral shedding.