Virology - Lecture 2

Last lecture we discussed Measles, Rubella and Mumps as childhood viral exanthems. Today's lecture is based on topics from the previous semester. We will be talking about:

1- Parvovirus B19
2- Human Herpes Viruses 6 & 7
3- Herpes Simplex Virus 1&2
4- Varicella-Zoster Virus

Please refer to the slides, the sheet doesn't cover everything

❖ Parvovirus B19 - Erythema Infectiosum (slides 24+25)

- Parvovirus is a **naked**, **ssDNA** virus with an **icosahedral** capsid.

- It's considered the **smallest** DNA virus.

- It's the ONLY virus that's **totally dependent** on the cellular machinery, as it **waits** for the cell to enter **the S phase** to use its machinery & enzymes for its replication, (can't induce the cell to enter the S phase, but only waits), (acts only on replicating cells). On the other hand, other DNA viruses **induce** cells to enter the S phase and use their cellular machinery.

- It uncoats in the **nucleus** (The whole nucleocapsid enters the nucleus). It has 3 capsid proteins: **VP-1, 2, 3**. Replication occurs in the **nucleus** (meaning: needs to infect nucleated cells).

-Cultured in bone marrow cells and fetal liver cells.

Erythema Infectiosum:

-Parvovirus B19 targets the **P antigen or globoside** as a receptor. Target cells are **nucleated** cells derived from **Erythroid progenitors** such as: Erythroblasts/ megakaryocytes / endothelial cells.

-Replicates in the nuclei of **immature** erythrocytes (immature RBCs, while mature ones aren't nucleated, so they're not a target) and copes with **minimal symptoms** (unless the patient has any preexisting blood disorder (e.g.: Thalassemia), then the illness will be more sever).

Incubation Period: 2-3 weeks.

Symptoms: Patients, who are immuno-compromised by such blood disorders, might present with fever only, but upon investigation, they were found to have **anemia and aplastic crisis**.

* If an immuno-suppressed patient –specially AIDS patient- shows up with an aplastic crisis or bone marrow failure we should suspect Parvovirus B19 infection.*

Patient shows other non-specific symptoms like fever, malaise, headache, myalgia and itching. The most important symptom is an **indurated rash on the face** (indurated: lacey or feels like a knit wear) that resembles **slapped cheeks**.

-The rash goes through **3 phases**:

1- Slapped cheek appearance (redness/erythema on both cheeks).
2- The rash spreads to the trunk.
3- The rash becomes indurated (lacey).

-May spread to lymph nodes & cause **Hepatosplenomegaly** (enlargement of the spleen and liver).

-Illness/rash lasts for **1-2 weeks** and the **redness disappears**. Rash may recur within **1 month- 5 weeks,** after the infection due to factors like (emotional stress/ heat/ sun light/exercise ...). Can be associated with infection of the endothelium and the joints.

Rare Complications: Hepatitis, Thrombocytopenia, Nephritis, Encephalitis.
Main Route of transmission: spreads by aerosols/droplets (**through respiratory route**). It's common in spring months, but still can be seen all the year.

Diagnosis: by PCR and serology using IgM specific antibodies against Parvovirus.

Treatment: no definitive treatment, but immune-compromised may benefit from IV immunoglobulins.

❖ Human Herpes Viruses 6&7 - Roseolla Infantum (refer to slide 27)

- HHV-6 has two variants: A&B. Variant B is associated with Exanthem Subitum.
- These viruses exhibit latency, target cells of the disease (where the virus replicates) are **CD4 T-lymphocytes** in both acute and latent infections.

- HHV-6 A&B are associated with **febrile illness**, which could be accompanied by seizures or not.

* Febrile illness with seizures -especially seen in infants- is known as febrile convulsion, results from a quick/sudden rise in temperature -to 40^{o} by 30 minutes- causing seizures. Antibiotics & cold water help in such case. But if it's the first time, Roseolla Infantum is **benign** in most cases.

Symptoms of Exanthem Subitum: **fever** (38.5^{o} -39^{o}) in **3-5 days**. **Faint macular rash** that **blanches** (meaning it disappears once touched). Starts on trunk and spreads to extremities.

- Manifestation mimics: EBV, Adenovirus, Coxsakievirus ... (**therefore diagnosis isn't easy**)

-Latent infection (stays in T-lymphocytes), so it might be reactivated with immunosuppressive status.
Diagnosis: culture, PCR, seroconversion between acute and convalescent sera 4 fold rise.

Treatment: **Ganciclovir**, but if patient is resistant to it, we use **Foscarnet**.

the tables in the following slides summarize everything the doctor has covered

❖ Herpes Viridae (refer to slide 2+3 in the 2nd slides)

- Enveloped, dsDNA virus with an icosahedral capsid. It has a **unique envelope.**.. WHY?

Because it's acquired from the **inner lamella of the nuclear membrane**. (Not from the plasma membrane)

-Capable of infecting **non-replicating cells**, as it has its own enzymes which induce the cell to enter the S phase. *Remember: Parvovirus only infects replicating/dividing cells.*

-Homology between **HSV-1 & 2** is 50%-70%, and between **HSV and VZV** is around 30%-50%. Has at least **9 glycoproteins** embedded in the envelope; which aid in the entry of the virus into the target cells.

-Under the electron microscope, the different types of HV cannot be differentiated. Its structure is a dsDNA enclosed by an icosahedral capsid, which is surrounded by a tegument (a protein filled space) then an envelope.

-Herpesviridae family are divided into **3 subfamilies** -according to the similarities- :

1- Alpha: HSV-1, HSV-2, VZV
2- Beta: CMV, HHV-6, HHV-7
3- Gama: EBV, HHV-8 (Kaposi Sarcoma)

Alpha group infections result in **painful skin lesions** that may ulcerate and heal without leaving any scars. Rare complications can happen like **encephalitis** (mainly by **HSV-1& VZV**), and HSV-2 is more associated with **meningitis.**

-Humans are the only natural hosts of HSV.

Latency of Herpes Viridae:

Means that after an infection the virus isn't completely cleared from the body, it goes to a certain type of cells, and then the DNA of the virus lies in the cells as an **episome** (circular DNA that isn't incorporated within the cellular genome). **Target cells during latency:**

Alpha group-> Nerve ganglia, **HHV-6&7**-> T-lymphocytes, **Kaposi's sarcoma**-> Tumour cells

*A part or whole of the genome is present in the cell. An episome is **NOT integrated** in the cell's genome, meaning there is **NO expression of early & late proteins (no enzymes for replication – Thymidine Kinase & DNA polymerase- and no structural proteins).** Only **immediate early proteins are expressed** and are necessary for early stages of replication.

That's a very important point in understanding why Antiviral drugs are not effective against latent Herpes Viridae, and that is because Thymidine Kinase (the target for antivirals) is not expressed in the latent cells.

-Due to latency the virus reactivates and causes a **re-infection** due to some triggers like: emotional stress, UV light, sun exposure, immune suppression, trauma... etc. Recurrence can also

be in immuno-competent individuals, by **the age of 50-60** (e.g.: shingles); due to suppression in the virus-specific-immunity against VSV (in case of shingles).

- Most of the time in HSV-1 & 2, manifestations of an infection result from the recurrent infection, because the primary infection usually passes unnoticed/patient is asymptomatic.

The 2 theories for reactivation:

- **The Skin Trigger Theory:** Chronic slow replication of the virus, and as a result, there is intermittent shedding of the virus into the skin.
- **The Ganglionic Theory:** Change in the metabolism of the cell/nerve, causing reactivation of the virus & appearance of the infection.

The Herpes Virus replication cycle:

1-Glycoproteins bind to receptors on target cell. (HSV receptor is **Heparan Sulfate**)

2- Virus is internalized into **the cytoplasm**, and it uncoats there. *Remember: Parvovirus uncoats in the nucleus*

3- DNA goes to **the nucleus** and acquires a circular form, 3 distinct stages of replication/protein synthesis:

A. **Immediate early stage**: No replication of the genome in this phase, only transcription and translation of trancriptases and replicases. (Once early stage starts, IE stage shuts off.)
B. **Early stage**: Non-structural enzymes (e.g: Thymidine kinase, DNA polymerase...), **genome replication starts** at this stage.
C. **Late stage**: transcription & translation of structural proteins (glycoproteins, capsid proteins...) takes place, occurs in the **cytoplasm**.

4- Using **DNA polymerases**, the genome multiplies and new copies of the genome are made.

5- The **structural proteins** move to the nucleus where the copies of the genome are, assembly occurs there. They exit acquiring **envelope from the inner lamella of the nuclear membrane**.

6- They go to the cytoplasm, and then leave the cell.

❖ **HSV-1 & HSV-2** (refer to slides 4+5)

HSV-1	HSV-2
Above the waist, can cause genital infection too.	Below the waist (70%)
By the age of 30, **90%** of people would have it's seroconversion (due to previous exposure)	Requires sexual activity, so at the age of 20 only **15-30%** would have it's seroconversion
Latency is in the trigeminal, superior cervical and vagal nerve **ganglion**	Latency is in ganglia of the sacral region S2,S3

Can travel to CNS and cause **encephalitis;** as a result of reactivation.	Can cause **meningitis**

Acute infection of HSV has the ability to form **multinucleated giant cells** (syncytia).

Pathogenesis: The virus spreads locally -> primary viremia -> virus disseminates to other organs -> replication -> secondary viremia -> after the acute phase, virus is not cleared out of the body -> craniospinal ganglia -> latency achieved.

Clinical Manifestaions: **refer to slides 6-13 I will only add the points that aren't in the slides***

Acute Gengivostomatitis, Ocular Herpes, Herpes Labialis by: **HSV-1**

Genital herpes (more with HSV-2), encephalitis, meningitis, neonatal herpes by: **HSV-1&2**

1- **Acute Gengivostomatitis:** it can be the primary manifestation of the **symptomatic** acute infection, but isn't always caused by viruses so might be missed. (check slide 7)
2- **Herpes Labialis (cold sores):** the most known presentation -by **45%-** is caused by recurrence of the **HSV** infection. Starts as a macule -> vesicle -> pustulates -> forms a crust -> heals without a scar in 1week-10days.
3- **Herpetic Whitlow**: *could be missed for bacterial infection* (the doctor read slide 8)
4- **Ocular Herpes:** rarely associated with blindness (slide 8)
5- **Herpes Simplex Encephalitis:** Tested by **PCR** of a CSF sample, if confirmed, IV acyclovir must be given, patients benefit from it. (the doctor read slide 9)

((Note: IV acyclovir is administered empirically until the PCR confirms the results; since the drug is relatively nontoxic, the prognosis for untreated HSE is poor, and delaying the treatment until the lab confirms will increase the mortality risk.))

6- **Genital Herpes:** mainly by HSV-2. (check slide 10)
- Lesions start as an erythmatous papule -> vesicle -> pustule -> heals without any scarring.
- Shedding of the virus (it is replicating) with no symptoms is very common in females.

Dysuria: burning sensation during urination

7- **Neonatal Herpes:** associated with high mortality rate, premature rupturing of the membranes is a predisposing risk factor caused mostly by HSV-2, when the infant passes through the birth canal, he might get infected with HSV-2. Brain is mostly involved, leading to meningitis or meningoencephalitis**. Acyclovir** would be helpful. (slide 11)

Laboratory diagnosis: (Check slide 12)

Tzanck Test: specific for Herpes Simplex Virus, it looks for **INTRAnuclear inclusion** (not internuclear, correct the slide), **Serology**: rarely used to diagnose HSV.

Management: (Check slide 13) Acyclovir, Famciclovir, Valacyclovir are all very useful once HSV infection is confirmed by lab tests. **There is no vaccine**. You can only consult people about safe sexual practices & screening pregnant mothers for HSV-2, if infected, delivery should be by C-section instead of normal vaginal delivery.

- **Varicella-Zoster** (please refer to slides15-19)

Acute infection	Recurrent infection(sensory nerve)
Varicella or Chicken pox	Zooster or Shingles
Common in Spring and Winter	Any time of the year; as a result of reactivation
Wide vesicular rash (everywhere)	On one side of the body, along with the dermatomes (superficial innervations of the skin)

-This virus has **one antigenic serotype**; infection once confirms lifelong immunity

-Highly communicable (75%-90%) *other highly communicable viruses are **Measles (95%) & HSV-1***

-**90%** seroconversion by adulthood (acquired immunity against Varicella)

Chicken Pox – Varicella:

-Communicability: Child is infectious from **1-2 days** before the appearance of the rash to **3-4 days** after the rash.

- Transmission: **respiratory route**, but also contact with skin lesions might spread the disease.

Like most other childhood exanthems, virus starts at upper respiratory track -> lymph nodes –> blood **(1ry viremia)**–> reticular endothelial system or spleen -> replicates -> blood **(2ry virema)** -> skin and by the time it reaches the skin, **antibodies (humoral immunity)** are formed.

- Incubation period of chicken pox: 2-3 weeks.

-Symptoms of chicken pox: fever, enlarged lymph nodes, wide vesicular rash.

Chicken pox rash is characterized by **different stages** of development. *in contrast to **small pox,** which its whole rash is in the **same developmental stage**.

-Complications: very rare, more common in **immuno-compromised patients**. **Adults** who get chicken pox at a late age have more severe symptoms than during childhood. The most common complication is **Bacterial Super Infection** due to multiple lesions (10s-100s) that are itchy, and

the child might scratch them, so they might form wide ulcers that will result in a bacterial super infection. **Encephalitis** is a very rare possibility too.

- Most of the time, reactivation of the virus after latency results in shingles.

Shingles (slide 20): Virus can travel along the dermatome, and can be associated with **Post Herpetic Neuralgia** (severe burning pain that results from virus travelling down & replicating within the nerve) that should be treated with strong anti-inflammatory drugs or pain killers.

We have 3 cases for pregnant mothers (Neonatal Varicella) (slide 22) :

1) Pregnant mothers **infected with Varicella**, the virus can cross the placenta and infect the fetus, resulting in congenital abnormalities.
2) If mother becomes infected with varicella **one week or more** before giving birth, the immunity is transferred to the fetus.
3) If mother is infected with varicella **less than a week** before delivery, an immunoglobulin should be given to the newborn immediately after birth.

Diagnosis (slide 23+24): similar to HSV (except Tzanck test) (doctor skipped slide 24)

Treatment (slide 25): in the case of **chicken pox** there is no need for treatment (immunity is acquired as soon as the rash appears –once the patient is symptomatic, Igs are formed-), you don't need to give Igs or specific antiviral drugs, but can treat it prophilactically upon exposure with Igs. In the case of **shingles** patient might benefit from **Acyclovir** treatment (topically or systematically or both together.)

Vaccination (slide 26): 1) Part of **MMRV**: given at 12-15 months, booster dose at 4-6 years.

2) **Live attenuated vaccine alone:** contraindicated in immuno-compromised patients (check the reason in the slides), can be given as prophylaxis against shingles (reactivation of the virus) for individuals >50 years old.

HHV-8(Kaposi's sarcoma): in AIDs patients, **acute** infection in **B cells, latent** infection in **Tumor cells**. No antiviral treatment. (Doctor read slide 28).

Look up a quote? Ain't nobody got time for that!