Reproductive Block

Lecture – 3

Genital Herpes & Genital Warts

Microbiology Team - 430

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❖ ***Introduction:***

- *Genital Herpes and genital Warts are recognized as the main sexual transmitted viral infections that might be acquired by any types of sexual contact.*
- *Risk groups:*
  1- *Adults who have multiple sexual partners.*
  2- *Immune compromised individuals.*
  3- *Infants who have infected mothers.*
  4- *Sexual child abuse.*

Genital herpes

*A viral STD caused by **HSV2**. Transmitted by **sexual contact**, also it can be transmitted from **mother to fetus**; 85% during delivery and 10% as vertical transmission during pregnancy. HSV2 enters the body and travels through nerve cells to **Sacral Ganglia**; in there it remains latent until it gets reactivated. Main symptom is appearance of herpetic vesicles in genital organs.*

Etiology:

- *There are two species of herpes virus capable of causing genital herpes:*
  - *Herpes simplex virus type 2 (HSV-2), 90% of cases*
  - *Herpes simplex virus type 1 (HSV-1) 10% of cases*

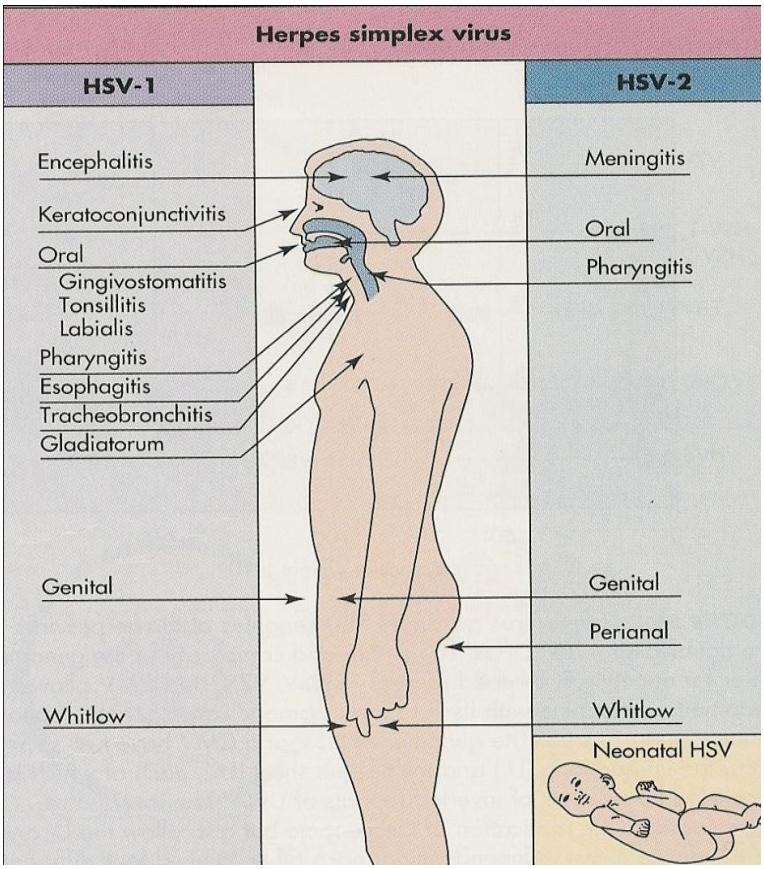
Characteristics of Herpes Virus:

- *Family of herpesviridae.*
- *Virion consist of:*
  - *Glycoprotein envelope*
  - *Icosahedra capsid.*
  - *Liner ds-DNA.*
- *The Herpes viruses has the ability to induce latent infection,*
- *HSV (1&2) travel in NERVE CELLS:*
  - *HSV-1 → Trigeminal ganglia (facial infection)*
  - *HSV-2 → Sacral ganglia (Genital infection)*

HSV type 1 & 2 enter the body → go to nerve cells.

- Type 1 goes to → trigeminal ganglia → causing Encephalitis
- Type 2 goes to → sacral ganglia → causing Meningitis

Both (HSV-1 & HSV-2) are structurally very similar and share about 70% sequence homology.



Transmission:

1- Sexual transmission:

- *The **number** of different sexual partners correlates directly with acquisition of HSV-2 in both male & female (more sexual partners, increases the risk)*
- ***Homosexual** men are more susceptible to HSV-2 infection (more in homosexual men)*
- *Genital infection can be acquired by **auto-inoculation** from lesions elsewhere on the body by touching vesicular fluids from any herpetic lesions (individual infect himself)*
- *HSV-1 can cause genital herpes infection after oral sex; also can be seen in cases of child abuse.*

2- Prenatal transmission (during delivery) 85%

- *The majority of maternal infection (85%) **occurs during delivery**, due to direct contact between the baby and infected maternal birth canal.*
- *The risk of prenatal transmission is usually occurred in about 50% of mothers have primary genital herpes, while the risk is 8% if mother have recurrent infection (risk is higher in primary rather than recurrent infection)*
- *This infection can lead to either massive herpetic skin lesions or generalized infection affecting skin and internal organs e.g.; lungs, liver or brain. (lead to neonatal herpes)*
- ***To avoid prenatal infection we do Caesarean section**.*

3- Intrauterine (vertical) transmission (10%):

- *Maternal **primary** genital HSV infection of the mother **during first trimester can leads to spontaneous abortion**.*
- *Maternal **primary** genital HSV infection which develops **after 20 weeks of gestations may induce malformation** as; microcephally, jaundice, Hepatosplenomegaly, Chorioretinitis and herpetic vesicles on the skin.*

Pathogenesis of HSV-2:

- *Primary infection occurs when HSV-2 infects epithelial cells covering the mucosa.*
- *The virus then migrates to the nearest ganglion (sacral ganglia) via neurons where it replicates and establishes latency for life.*
- *Once it's reactivated, it travels back through neurons to the site of the primary infection and causes recurrent infection.*

**** Once the virus enters the human body it remains for life (latency)***

- ***HSV-2 infects epithelial cells covering the mucosa → Migrates to the sacral ganglion → replicates and establish latency for life. (Primary infection).***
- ***Reactivated → goes to the site of primary infection → via neurons. (recurrent infection)***

Clinical features:

❖ *Primary genital herpes:*

- *Vary from asymptomatic to mild or severe painful episode.*
- *If symptoms are present(**I.P 2-12 days**) they may include;*
  - *fever , malaise, Dysuria,*
  - *Inguinal lymphadenopathy.*
  - ***Vesicular herpetic lesion** or ulcer localized to the cervix, vagina, vulva or perineum of the female or the shaft of the penis in the male, herpetic proctitis can be seen in homosexuals.*

- *Aseptic meningitis has been observed in about 10% of cases as extra genital presentation.*

❖ ***Recurrent genital herpes:***

- *Occurs after reactivation by environmental or physiological factors such as stress, exposure to U.V. light, menstruation, pregnancy or any condition* ***decreases the immunity.***
- *This can be as frequent as six or more episode a year; the attacks are milder and shorter than primary episode.*
- *Accompanied with appearance of herpetic vesicles on external genitalia, and may include pain and itching.*

Neonatal herpes infection: *(not common, but the mortality is >70%)*

- *It occurs during labor and delivery (more likely 85%), or as vertical transmission during pregnancy (less likely 10%)*
- *It may spread to other organs such as lungs, liver, brain (generalized infection)*
- *It has three forms:*
  - *1-* ***Localized skin infection:*** *limited to massive skin vesicular lesions (mild infection)*
  - *2-* ***Localized brain infection:*** *limited to CNS invasion causing encephalitis (mortality is high)*
  - *3-* ***Generalized neonatal herpes infection:***

  Severe massive infection of the skin accompanied with internal organs infection as lungs (pneumonia), liver (Hepatosplenomegaly), and brain (encephalitis) with massive skin herpetic lesions (Usually fatal)

Lab diagnosis:

1. ***Tissue culture:*** *(Vesicle fluid sample is cultured by scraping the base of the vesicle)*
   We look for CPE (Cytopathic Effect: degenerative changes in the cell)
2. ***Direct IF:*** *(Same sample after noticing CPE we do Direct Immunofluorescence)*
   We detect the Antigen (Ag)
3. ***ELISA:*** *(Sample is serum)*
   We detect Ab (IgM), it's a routine test
4. ***PCR:*** *(Sample is CSF "requires very small amount")*
   Best technique, but very expensive, we do it in case of neonatal herpes

Management:

- *No vaccine is available to prevent HSV-2 infection, and thus the best way to control the HSV infection is by:*
  - *Avoid sexual contact with infected individuals.*
  - *Abstain from making prohibited relations.*
- *Note: Condoms are not 100% protective against genital herpes infection.*

Treatment:

- ***Acyclovir:*** *1st choice therapy, suitable for pregnant women.*
- *Famciclovir.*
- *Valacyclovir.*

Genital Warts

*A viral STD caused by **HPV** which has more than 100 genotypes. HPV mainly causes two types of infections; **cutaneous** and **genital**. HPV **types 6 and 11 are benign** and cause Condyloma acuminate. Types **16 and 18 are oncogenic** and might progress to cervical cancer. Main symptom is appearance of **warts** in the genital area.*

Etiology:

- *Humanpapilloma virus (HPV)*
- *There are more than 100 genotypes of HPV*

Characteristics of HPV:

- *Family of Papillomaviridae.*
- *Virion is small non-enveloped, and consist of:*
  - *Icosahedra capsid.*
  - *Circular ds-DNA.*
  - *They cause disease only in skin (cutaneous) and mucous membrane (genital)*
- ***Does not grow in tissue culture.***
- *Resists detergent and heat and can remain infectious in the environment for long time.*

Types of warts and HPV genotype:

Cutaneous warts	***Genital Warts (Genital, Anogenital or mucosal Warts)***
Common Warts (HPV types 2,4)	***Condyloma acuminate (benign HPV 6,11)***
Plantar Warts (HPV types1,2,4)	***Cervical carcinoma (Oncogenic HPV 16,18, 31,45)***
Flat Warts (HPV types 3, 10)	*Penile and anal carcinoma (HPV 16, 18) in men.*
	Laryngeal Warts (benign HPV 6, 11).

Transmission:

- ***Cutaneous Warts***
  - *Direct contact hand to hand (common warts) or via fomites and abrasions*
  - *Swimming pools and changing rooms are fertile sources of infection; cutaneous warts are most liable to affect young children.*
- ***Genital Warts***
  - *Sexual contact (more sexual partners, increases the risk) and it may occur with other STDs such as Gonorrhea or Chlamydia infections.*
  - *Vertical transmission from mother to infant prenatally within the first 6 weeks of life has been demonstrated.*
  - *They might be transmitted to baby during delivery*

Clinical features of genital HPV infection (Genital Warts):

- *Appear after 3-4 months after infection (I.P).*
- ***Warts** (small, benign growths) size varies and found in the Anogenital tract (inside or outside the genital and the anal areas of both males and females).*
- *Localized pain, Discomfort and sometimes abnormal vaginal bleeding and discharge.*

Link between HPV and cervical cancer:

*Persistent **HPV infection is considered the main cause of cervical cancer**; HPV DNA can be detected in most grades of premalignant lesions of the female and male genital tract.*

***HPV type 6 and 11**(Condyloma acuminata) are **benign**, but they might progress to squamous cell carcinoma.*

HPV 16 and 18** are more commonly associated with dysplasia which involves all layers of stratified epithelium, and has high chance of progression to metastasizing carcinoma & invasive cancer. **(malignant/oncogenic)

Pap-smear: is a screening test for detection of cervical carcinoma, > 90% of positive Pap-smear is due to HPV infection

Diagnosis:

- *External genital warts can be easily diagnosed by medical examination.*
- *Internal genital warts can be visualized by colposcopy. (procedure to examine the vagina and cervix)*
- *Lab diagnosis:*
  - *PCR is used to detect HPV DNA. (first choice)*
  - *In-situ DNA hybridization is used for HPV genotyping.*
  - *Pap-smear test is used to identify abnormal epithelial cells of the cervix (cervical dysplasia).*

Pap smear do not detect HPV, it is a diagnosis method for cervical cancer, which HPV is the main cause for it

Treatment:

1- ***Cryotherapy**: (freezing warts by liquid nitrogen)*
   - *suitable for small external warts*

2- ***Elctrocautery treatment**: (destroying warts by an electric current)*
   - *suitable for small warts*

3- ***Laser therapy**: (destroying warts by a focused light beam)*
   - *suitable for small and large warts*

4- ***Surgical excision**: (removing warts by surgical tools)*
   - *suitable for all warts*

5- Topical treatment:
   - *Imiquimod, Podofilox (applied directly on external warts and used for several weeks)*
   - *Podophyllin (applied by a doctor and contraindicated in pregnancy)*
   - *Trichloroacitic acid (T.C.A) safe in pregnancy.*

6- ***Injection** of Interferon alpha or 5-flurouracil epinephrine gel.*

Prevention:

*There are two vaccines available **Gardasil** and **Cervarix** and both are:*

- *Recombinant viral-like particles with no DNA.*
- *Given in 3 doses at 0, 2, 6 months.*
- *Recommended for young individuals ages 9-26 yrs old and are **not given to pregnant women**.*

❖ ***Gardasil**, a quadrivalent vaccine, provides protection against HPV genotypes 6,11,16,18 which causes genital warts.*

❖ ***Cervarix**, a divalent vaccine, provides protection against HPV genotypes 16, and 18 which causes cervical cancer.*

Summary

- *There are two types of HSV 1&2 both has ds-DNA, 90% of genital herpes infections caused by type 2*
- ***HSV-1*** *travel through nerve cells → Trigeminal ganglia (stays latent or facial infection) → Encephalitis*
- ***HSV-2*** *travel through nerve cell → Sacral ganglia (stays latent or Genital infection) → Meningitis*
- *Once the virus enters the human body it remains for life (latency).*
- *HSV-2 get transmitted by sexual contact or maternally; 85% during delivery or 10% as vertical transmission*
- *Primary infection of mother has more risk to get transmitted to the baby during delivery, to avoid it we do C-section*
- *If vertical transmission occurred during 1st trimester it can lead to spontaneous abortion, and if occurred after 20 weeks malformations in fetus might be present*
- *If the infection got transmitted during delivery (85%) or during pregnancy (10%) to the baby it is called* ***neonatal herpes***
- *Vesicular herpetic lesions in the genital area is the clinical picture might be with inguinal lymphadenopathy*
- *Lab diagnosis is done by:*
    - *Tissue culture (Vesicle fluid sample taken by scraping) → CPE in cells*
    - *Direct IF (Vesicle fluid sample taken by scraping) → HSV-2 Ag*
    - *ELISA (serum sample) → Ab e.g. IgM*
    - *PCR (CSF sample) → we do It in case of neonatal herpes*
- *No vaccine is available to prevent HSV-2 infection, and 1st choice therapy is* ***Acyclovir***

- *HPV has more than 100 genotypes and causes cutaneous (skin) and genital (mucus membrane) infections*
- *HPV has ds-DNA, and it* ***can't grow by culture****, and it resists detergent and heat so it remains infectious in the environment for long time.*
- ***Warts*** *(small, benign growths)in the Anogenital tract are the main symptom for genital warts*
- ***90% of positive Pap-smear cervical carcinoma are due to HPV infection***
- *Types 16 and 18 are oncogenic types (malignant) and progress to* ***cervical cancer***
- *Types 6 and 11 are benign types and cause* ***Condyloma acuminate*** *(genital warts)*
- *External infection can be diagnosed by clinical examination, Internal infection by colposcopy*
- *Lab diagnosis:*
    - *PCR → HPV DNA. (first choice)*
    - *In-situ DNA hybridization → HPV genotyping.*
    - *Pap-smear test → abnormal epithelial cells of the cervix (cervical dysplasia).*

- *There are two vaccines available* ***Gardasil*** *and* ***Cervarix*** *and both are contraindicated in pregnancy.*
- ***Gardasil*** *provides protection against HPV genotypes 6,11,16,18 which causes genital warts.*
- ***Cervarix****, provides protection against HPV genotypes 16, and 18 which causes cervical cancer.*