Microbiology

◉ Sheet ○ Slides

Number : 5

Done by Mohammad Qussay Al-Sabbagh

Subject: Virology (pathogenesis)

Doctor: Dr. Sammer Naji

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Pathogenesis of viral infection :

Welcome to Virology *sheet 5* , also known as *pathogenesis of viral infection notes* , here we will explain some critical points (dr. Sammer lecture + some notes from dr.Ashraf)… make sure that you fully understand this important concept , because all virology depends on this lecture !

Remember , the main source is the slides , this is just notes …

So turn off the Internet , notes are here , the slides are ready , let's get the party started .

❖ Slide 1

Some terminology ..

● **Endemic**: Disease present at fairly low but constant level .. **مستوطن**

Ex : *malaria , bilharzia* ; all these illnesses are endemic and we can label that certain countries are endemic for these infections .

● **Epidemic**: Infection greater than usually found in a population ..

Simply , Change in the number of cases infected with the virus in certain location in a certain period of time , this is epidemic Ex: *influenza* as well as *common cold* increase in the winter months ; influenza come in epidemic each year .

●**pandemic:** Infections that are spread worldwide… **وباء عالمي**

The infection starts in certain location then spread worldwide . Ex: : corona (SARS , MEREs) is an pandemic infection that spread worldwide.

● **infectivity:** The frequency with which an infection is transmitted when contact between a virus and host occurs ..

what does this mean ?

A: When we have person A & person B ,infectivity is the frequency by which the infection is transmitted from person A to person B , EX : when we are talking about disease like measles (highly infectious virus) ; the chance of the healthy person to get the infection from infected person is (90 to 95 %) this is the infectivity .

● **Disease index:**

Here , we have certain infection , and infected people . We have two groups of infected people : **subclinical** and **those who have symptoms** .

So , disease index is the number of those **who have symptoms** / **total number** of those who are infected . because it is not easy to know the number of totally infected without doing serological test , This is a hypothetical measurement .

● **Virulence**: Number of those who have the disease and **died** with disease / **total number** of those who have the disease .

incidence & **prevalence** , these two terms come together as well ..

● **Incidence**: Number of new cases at a **certain geographical** point , most of the time given as a **percentage** of (number of new cases / number of the present cases) .

● **Prevalence**: number of cases of a disease that are present in a particular population at a given time (we are talking about a **number**)

Ex: If the number of the new cases of *HIV* in Jordan is 330 case/year , and the actual number of the cases at this year is 1000 , what's the prevalence , and the incidence ?

prevalence → is the total number of cases = 1000

incidence → the new yearly cases = 330/1000 = 33%

❖ Slide 2

What does the pathogen have to do ? – ما هي وظيفة الفايروس من وجهة نظر الفايروس–

Infect a host , Reproduce itself and Ensure that its progeny are transmitted to another host .

❖ Slides 3 + 4

how can the virus be transmitted among humans .

1. Horizontal: (person to person)

A. **Inhalation-**via the respiratory tract (aerosols or droplets) , ex : RSV (Respiratory syncytial virus) , MMR (Measles, Mumps, & Rubella) , VZV (Varicella zoster virus) and Rhinovirus
B. **Ingestion :** via the gastrointestinal tract (fecal – oral route)

● **NOTE** : the viruses that cause **gastroenteritis** or **their primary route of infection is the GIT** through fecal-oral transmission are **naked viruses , why ?!**

we know previously that the naked viruses are superior to the enveloped viruses because they can tolerate the environmental and the acidity of the stomach and the sterilizing effect of the bile salts , in contrast the enveloped viruses can not tolerate the acidity of the stomach and once they arrive there ,they will be destroyed .

EX : when we said **hepatitis A** ,the virus is transmitted via the fecal – oral route , primary replication occurs in the GIT then viraemia then goes to the liver cells .

Other examples given here (**Rota, Astroviruses , Caliciviruses**) the infection is limited to the GIT causing **gastroenteritis .**

C. Inoculation … (read the slides :p)

2. Vertical : from mother to fetus ☹

we have three different stages through which the transmission can occur ... these stages are :

Transplacental (during pregnancy) , Delivery and Breast feeding (after delivery) , read the examples .

3-zoonotic : from animal to human , (Animal bite , insect bite and animal excreta)

❖ Slide 5

● **Incubation period: (فترة حضانة الفايروس)** Time between exposure (the entry of the virus) and first symptom .

● **Gastroenteritis viruses** & **common cold viruses** have **short** incubation period , which might range from 12hours up to 5 days .

● We have viruses such as the **hepatitis** viruses which have **intermediate** incubation period, we are talking about weeks to six months .

● we have viruses that have **long incubation periods** such as **rabies & HIV** , IN rabies we are talking about one day to one year , and if you treat the rabies before the symptoms develop then the patient is going to survive ,but once the patient is symptomatic with rabies then the patient will die within 2to 3 weeks ,IN HIV , the incubation period from one year up to 10 years !

❖ Slide 6 , 7 , 8 and 9 → the slides are enough

Just to summarize :

●Site of of entry → regional LN → blood (primary viremia)→ organs (liver, spleen) , & replicates in these organs → blood (secondary viremia)

●Usually **secondary viremia** results in higher viral shedding and viral loads within the bloodstream due to the possibility that the virus is able to reach its natural host cell from the bloodstream and replicate more efficiently than the initial site .

● Primary viral replication → localized infection

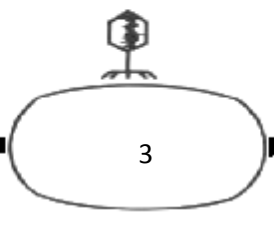
● Secondary viral replication → systemic infection → disease

❖ Slides 10 , 11 and 12

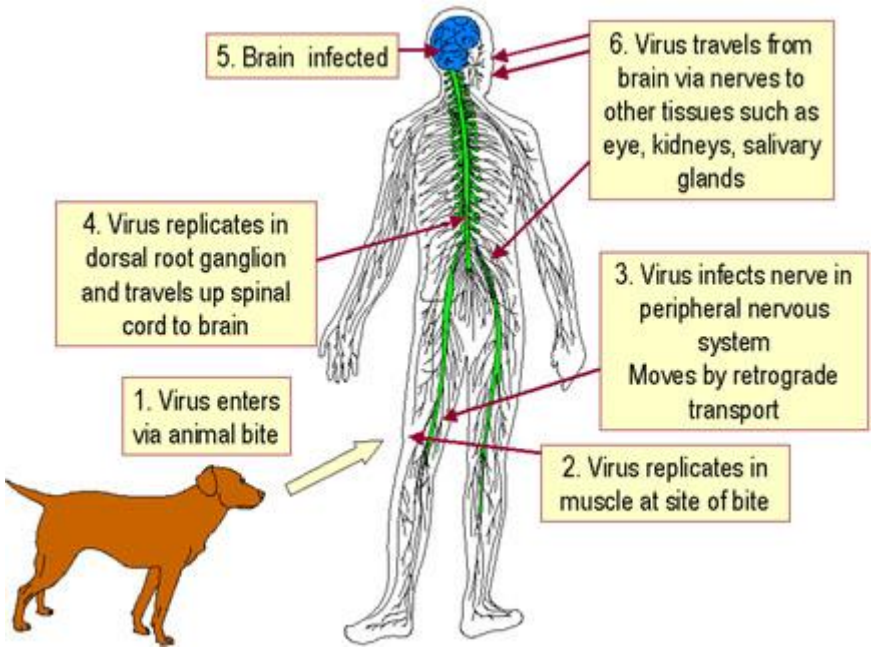
there are 2 main mechanisms for spread throughout the host: **via the bloodstream or via the nervous system** , now refer to the slides for the definitions , and read these examples :

1-many viruses uses bloodstream (secondary viremia as mentioned)

2-rabies (داء الكلب) :



Locally at the bite site , we have a **primary replication** of the virus and while the muscles and nerves might be involved in the bite , primary replication occurs in muscles and then it is going to travel along the nerves until it reaches the central nervous system ,once it reaches the central nervous system the patient became symptomatic and he is going to die , now this variation in incubation period from one patient to another depends on the site of the bite ; which means that ;a patient with a bite in his leg will differ from a patient with a bite in his neck , because the incubation period in the second patient (neck bite) will be shorter than the incubation period in the first one (leg bite) , because the virus in the first case needs longer time to reach the CNS than the second one **. (Via nervous system)**



3- Herpes simplex virus :

the virus will infect then hide in a latent (dormant) form , Now In Herpes simplex virus 1 & 2 and varicella-zoster virus , the cells of latency will be the nerve ganglia (the virus is latent in the nerve ganglia) then reactivation of the virus occurs by traveling of the virus from the cells where it was dormant in along the nerves until it reaches the skin or mucous membranes **. (Via nervous system)**

❖ Slides 13 → 16

● **Virulence**: the ability of the virus to cause disease in infected cell

● Some viruses , causes **Persistent infection "**means that the virus will stay forever :'(**" ,** is divided into :

-Latent infection, lysogeny -Chronic infection

● **Virulent viruses** : Kill target cell and cause disease (**productive** response)

● ***Abortive infection*** no virus replication, early viral proteins cause cell death (remember from pathology , some cells are smart enough to undergo apoptosis once they are infected by a virus , to prevent viral pathogenesis :p)

● ***Permissive cells*****:** are the cells that allow the production of the virus. (If the virus comes into contact to those cells, the virus is going to be internalized and capable of replication and producing new viruses). They are associated with **virulent** viruses.

● ***Nonpermissive cells*** **"**the smart cells " 😎 : permits cell transformation only , the virus might inter into the cell, but it is not going to be able to complete its replication cycle. THEY are associated with **abortive infection**.

Note : not all nonpermissive cells undergo apoptosis , some of them will be transformed to cancerous cells for example !!!

SooOo :

● If the virus infected a **permissive** cell → it is labeled as **virulent** virus → it is going to replicate itself → kill the target cell (kill target cell means it is an acute lytic infection). → Cause disease. (productive response because the virus is going to replicate and produce new viruses)

● If the virus infected a **Nonpermissive** cell → **abortive** infection (no viral replication), we may see only early protein synthesis (viruses are not going to complete their replication) → the presence of these viral early proteins might lead to transformation of the cell

● **Cytopathic effects** : virus-induced damage to cells .

● **what is the range of cytopathic effects that we can see in the cells?**

I. Changes in size & shape
II. Cytoplasmic inclusion bodies
III. Nuclear inclusion bodies

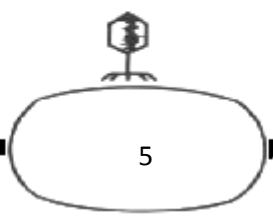
Wait wait wait … what do we mean by inclusion bodies ?

Inclusion bodies are : clumping of the viral capsid proteins , in another words they are the aggregation of the capsid proteins of the virus .

- Mmmmm oki , but what determine whether the inclusions are in the cytoplasm or in the nucleus?

DNA viruses replicate in the nucleus , that means that when we talk about nuclear inclusion bodies then we are talking about DNA virus infection, and when we are talking about cytoplasmic inclusion bodies we are talking about RNA virus infection and replication .

IV. Cells fuse to form multinucleated cells



- whaaaaat !! multinucleated cells !! what is the meaning of that , and how do we get it?

cells fuse together with the aggregation of multi nuclei within large cell , In this case we are talking about **enveloped virus infection** ; we all know that enveloped virus (such as HIV , Herpes viruses) enter the cell by **fusion** & leaves their envelope as a part of the cell membrane , now , Neighboring cells have receptors on their surfaces for the glycoproteins of the virus (glycoproteins that can be found in the envelope of the virus that is a part of the cell membrane now) , when these receptors bind with these glycoproteins (formation of glycoprotein-receptor complex) , the cells will fuse together as a result of fusion between the two membranes . “Cells are going crazy hhhh ”

V. Cell lysis
VI. Alter DNA
VII. Transform cells into cancerous cells
VIII. Virokines and viroreceptors: DNA viruses; cell proliferate and avoid host defenses .

Virokines -_- , what the hell is that !!!

A virokine is a protein encoded by certain viruses that acts as a competitive inhibitor of a host cytokines. As cytokines act as an essential part of a hosts immune system, virokines are used by viruses for immunomodulation and subverting host immune responses**.**

Notes about table 6.4

- herpes virus causes a nuclear inclusion because it is a DNA virus
- Adenovirus causes a nuclear inclusion because it is a DNA virus.
- Reovirus (Rotavirus that cause gastroenteritis)
- Rabies is an RNA virus that cause a cytoplasmic inclusions
- multinucleated giant cells in HIV virus

❖ Slides 17 → 21

Patterns of viral infection, the slides are enough , to summarize :

● **Acute infection followed by clearing** ; the virus enters the body & replicates, then as a result , symptoms develop and last for a short period of time (5,7,10 days) , followed by complete clearance of the virus from the body and the patient is no longer symptomatic , this is acute lytic infection .

● **chronic infection** ; the virus is still in the body and is not cleared ;we have to types of this infection :

1- when we are talking about hepatitis B infection : We have acute phase of the illness ..disease appears early after the infection .. the virus is still there its shedding & its replicating at a very slow base & its causing problems to the liver and our body .

2- we have chronic infections in which we see the disease later in the infection , example HTLV-1 (Human T-cell lymphotropic virus type 1 or human T-lymphotropic virus type 1 (HTLV-I), also called the adult T-cell lymphoma virus type)

● **acute followed by latent** ; the patient could have an acute phase (symptomatic) or primary infection that could be asymptomatic , example is herpes virus ; the patient might have a primary infection or acute infection then after that the patient will no longer have symptoms , because the virus goes and lie dormant in the latent cells.

❖ Slides 22 → 28

Overall fate of cells (what will happen to infected cells) ?

1-cell dies in cytocidal infections : ☹

this may be acute (when infection is brief and self-limiting) or chronic (drawn out, only a few cells infected while the rest proliferate)

2-The cell lives in persistent infections

this may be **productive** or **nonproductive** (refers to whether or not virions are produced) or it may alternate between the two by way of latency and reactivation - Steady state infection-

3-Transformation

- Transformation-Integrated infection (**Viruses** and **Tumor**)
- **Transformation means :** is the change from a normal cell into a cancerous cell .
- DNA viruses and RNA viruses can transform the cell

I. **RNA tumor viruses (ex : reterovirus)** : usually transform cells to a malignant phenotype by integrating their own genetic material into the cellular genome and may also produce infectious progeny ,

There are three mechamisms by which the retroviruses can induce transformation:

A) **Acute transforming viruses**: V-SRC oncogene mimic cellular genes (proto- oncogene) :

The SRC gene is a cellular **oncogenic** as it triggers uncontrolled growth in abnormal host cells. It was the first retroviral oncogene to be discovered.during evolution the SRC gene was taken up by a virus and incorporated into its genome conferring it with the advantage of being able to stimulate uncontrolled mitosis of host cells, providing abundant cells for fresh infection.

Note : An **oncogene** is a gene that has the potential to cause cancer.

B**) Insertional mutagenesis**: inappropriate expression of a proto-oncogene adjacent to integrated viral genome .

Porto-oncogenes : are cellular genes or cellular enzymes, they are important to regulate the cell function)

Oki you said cellular genes .. Where the virus has acquired these genes?

The presence of the virus for many years ,in infected humans → replicates inside the cell and as a part of replication there's something called ***(copy choice recombination***), during the replication of the virus we may have mutation caused by copy choice recombination.
It takes part of the hosts genes and integrate it or becomes part of the viral genes.

In the host → it is **proto-oncogenic**
In the virus → it becomes **oncogenic**

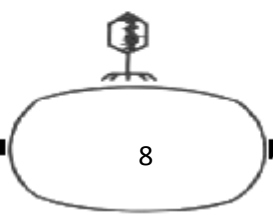
In the cell → it needs promoter before the proto-oncogene
in the viral form → it needs promoter before the virus

If the viral oncogene inserted in **front of the promoter** of proto-oncogene the cells promoter will express or translate (transcription & translation) of the cellular gene (the proto-oncogene of the cell), but the production (expression of the proto-oncogene) becomes uncontrollable and the cell will produce more amount of the proto-oncogene as a result of the promoter of oncogene inserted in front of the proto-oncogene.

C) **Trans activating factors**: tax gene in HTLV-1; turns on cellular genes causing uncontrolled cellular proliferation. Retroviruses: (HIV)

II. **DNA tumor virus**: infections are often cytocidal(cytocidal means that it ends by killing the cell);thus transformation is associated with **abortive** or **restrictive infections** in which few viral genes are expressed.

We have said that when we have DNA virus ,we have abortive infection , the virus **cannot** replicate or continue its full replication cycle within the cell, but it is capable of producing early protein , the presence of these early proteins might be transforming to the cell.



The persistence of **at least part of the viral genome** within the cell is required for cell transformation. This is accompanied by the continual expression from a number of viral genes.
Part or the complete genome of the virus stays or remains in the cell and the expression of the early protein only of the virus in conditions for latency.

The DNA viruses that are transforming viruses they are capable of latency (*herpes* , *human papilloma*) , and the latency can be in the form of episome (extrachromosomal -not integrated-) or it can be integrated with in the genome. Most of the times tumors associated more with virus being integrated within the genome, though they found that in cases of cancer an extrachromosomal episome was also associated with transformation of the cell.

- P53 ; regulates the cell cycle; functions as a tumor suppressor that is involved in preventing cancer.

- pRb (reteno-plastoma) : prevent excessive cell growth by inhibiting cell cycle progression until a cell is ready to divide.

These both are **genes** that regulates the cell cycle , the transforming viruses are capable of blocking the effect of both P53 and reteno-plastoma genes.

Note : the function of P53 is to Repair the DNA , if there is anything wrong in the DNA, and if the DNA repair is beyond repair then it would induce killing of the cell , ,so it will control the replication of the cell.

4- Apoptosis
- initiate apoptosis, programmed cell death, if DNA damage improved to be irreparable.

As a summary , Possible consequences to a cell that is infected by a virus are :
- lytic infections
-persistent infections
-latent infections
- transformation

I know I have mentioned a lot of information here .. I'm sorry ☹ , but believe me , this is the full explanation of what is written in the slides , and we are supposed to know all these concepts by details , Dr. Ashraf likes to ask about these things in Viral replication …!!!!

And here is virology quiz to test your self :

أصعب جزء خلال الدراسة قبل الإمتحان هو مرحلة المراجعة , لأنو خلالها بتكتشف أنك مش دارس ولا شي , و كنت بتشلفق و تضحك على حالك بس !!

بمزح بمزح هههههه .. يلا إلى الأسئلة

1) Which of the following can be transmitted to human :

A.Scrapie B.BSE C.Kuru D.All of the above E. A&C

2)which of the following is not a viral Feature:

A. obligate Intracellular parasite
B. inert filterable agents
C. viruses can make energy independent of a host cell
D. All of the above
E. None of the above

3)one statement is true regarding viroids :

A. cause diseases in plants only
B. are misfielded proteins
C. can be either DNA or RNA
D. none of the above
E. A & C

4) One statement is true regarding adsorption :

A. Enveloped receptors use surface groves to bind cellular receptor
B. A single receptor can be used by several viruses
C. HIV virus uses CD8 receptors
D. Occur only in naked viruses
E. None of the above

5) Regarding HIV , all of the following are true except :

A. It's RNA virus
B. Uses RNA dependent DNA polymerase
C. Causes chronic infection by inserting it's prophage in cellular genome .
D. Causes cell fusion
E. C & D

Answers :

1) **C**
2) **C**
3) **A**
4) **B**
5) **C**

عندما تشتد ظلمة الطريق , فاعلم أن الفَرَجَ قريب ...

فالعظماء يولدون من رحم المعاناة