INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	20
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Immunodeficiency

In this sheet we'll talk about the types of immunodeficiency and we'll concentrate more on HIV. There are two types of Immunodeficiency; hereditary and acquired.

Hereditary Immunodeficiency

It's rare and happens in 1/10,000 live birthsdue to hereditary causes mainly mutations. We have taken so many examples throughout the course, such as:

(Only few notes written about each example that was the mentioned from the doctor, if you want more information please refer to their original sheets)

1- Hyper IgM syndrome: It's an impaired class switching resulted from AID def, CD40L deficiency on the T cells and CD40 deficiency.
2- Di George syndrome: This is a deletion in 22q11.2 that leads to low numbers of T-cell.
3- SCID, severe combined immunodeficiency, that could be a result of many mutations (In our case it was an X-linked mutation in the common gamma chain) SCID can also results from ADA deficiency, Omens syndrome (RAG1 and RAG2 mutation)… etc.
4- Mutation in the complement system, such as C3 deficiency which is very rare.

Acquired Immunodeficiency

The person might acquire immunodeficiencythroughout their lives due to many reasons, most common ones are mentioned below:

1- **Malnutrition**: It's the main cause of acquired immunodeficiency; so good nutrition (such as Vitamin E and C, which both work as antioxidants) , doing exercise and weight reduction are good things to strengthen your immunity.

2- **Medication and Treatment:**(the second most common cause) Transplant patients are intentionally made immune suppressed by takingCyclosporine. But unintentionally cancer patients are immune suppressed byradiotherapy and chemotherapy.

3- **Infectious disease:** Most importantlyHIV " and we'll continue the whole lecture talking about it) and that's because it’s not curable so far and it presents with chronic immunodeficiency. While other infectious diseases presents mostly withacute

immunodeficiencythat will resolve after awhile. Measles also causes immunodeficiency, and it was known that anyone who had measles and Tb together willdie eventually! Note that Tb is usually latent but if the patient got immune suppressed (with measles for examples) this will be fetal.

Nutrition and infection

There is a strong relation between nutrition and infection and each one of them will lead to the other. Under-nutrition decreases the function of innate and adaptive immune system and that will lead to infections. On the other hand, infections cause mucosal injury, impaired absorption and blockage to the GI lumenwhich in turn lead to under-nutrition.

HIV

From now and on we'll be talking only about HIV, to make it easier, these are the aspects that will be mentioned, make sure that you know each one!

1- General idea about HIV and routs of transmission
2- Some numbers related to HIV
3- The virology of the virus
4- HIV-1 vs. HIV-2
5-Phases of HIV infection
6- HIV-1 vs. the immune system
7- Treatment
8- AIDS in mother and child
9- Lab tests for HIV**..***Don't panic they are short and easy and you know a lot about them.*

1- General idea about HIV and routs of transmission

HIV is very important as it's a challenge to immunologists with its increasing number of cases due to globalization by wars, migrations and the advancement in the transportation methods.This virus was previously known among the homosexual

people, and that's no longer the case as it's spread nowadays in both homosexual and heterosexual, and actually the cases of heterosexual nowadays are much more!

It can be transmitted in the previous method (sexual one), but it also could be transmitted by other ways; such as blood transfusion and needle use (which is common among drug users who uses unclean shared needle). And it also could be transmitted from the pregnant to her baby during pregnancy (through placenta) or during breastfeeding.

**Note: The transmission of the infection through blood transfusion has been decreased by applying the idea of blood screening before transfusion.*

**A note to future doctors: You will face children and innocent patients who didn't choose to have HIV and they need to be treated, so please don't look superiorly to them.*

2- Some numbers related to HIV

1) 37 million person is infected with HIV worldwide (according to WHO,2016)
2) 1 million die yearly of HIV despite the PRESENCE of treatment!And that's because some patients don't have access to the treatment (such as those in parts of Africa where the disease is most prevalent!!) and other patients can't afford its huge cost!
3) HIV-1 was discovered in 1981
4) Billion dollars spent yearly on HIV-1 researches and almost every large institute has special department for HIV.So it's a very hot topic!
5) It was discovered as it was highly associated with opportunistic infection like pneumocystiscarinii pneumonia and pneumocystis jiroveci and with rare cancers such as Kaposi sarcoma. (those diseases are usually seen with immune suppressed patients)

3- About the virology of the virus

It's an RNA virus that has Reverse Transcriptase enzyme (RT, that converts RNA to DNA) and surface molecules (known as glycoproteins). *In the next lecture we'll talk more about this section.*

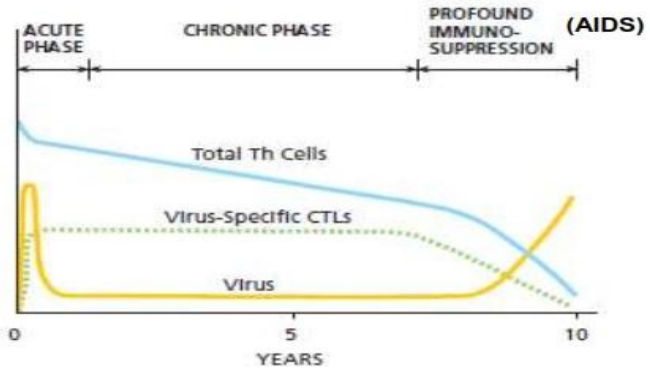
4- HIV-1 vs. HIV-2

There are two major types of HIV; (HIV-1 and HIV-2) they are very similar, but they differ in their DNA sequence and the way each one presents the disease.

- HIV-2 is usually restricted toWest Africa (you can findsome cases here and there because of globalization) and is usually less aggressive, has longer asymptomatic stage, lower plasma virus-RNA level and lower mortality. But don't forget that it's still an HIV virus and it will also go on and progress into AIDS also they need a modified treatment plane.
- More researches are done towards HIV-1 sparing the HIV-2 without the needed attention and well-defined optimal treatment.

5- Phases of HIV Infection

The infection is divided into 3 phases mainly, and they are well illustrated in the picture below (Blue line is the amount of T-helper cells, Yellow line is the amount of the virus and the green one represents the cytotoxic T cells).



These three phases are:

(1) Acute phase
(2) chronic phase
(3) Profound Immuno-suppression and AIDS.

1- ACUTE PHASE

At the beginning of the infection, the virus enters the body and the number of the virus is increasing. T helper cells will see the virus and it will activate cytotoxic T cells which in turn will start killing the virally infected cells. So the virus titers will decrease. This phase could be asymptomatic or have flu-like symptoms!

2- CHRONIC PHASE

In this phase, there is a competition or a war between the virus and cytotoxic T cells. T helper cells are still helping in activating cytotoxic T cells but their (Helper T cells) numbers are steadily decreasing. At this phase, we keep on monitoring the levels of helper T cells by flowcytometry until we reach a certain level, and at this certain level the patient will enter the next phase, which is AIDS.

3- AIDS PHASE

It's known by its huge decrease in number of helper and cytotoxic T cells; that's why the patient will enter profound immune suppression phase and they will be under treatment. (Keep in mind that HIV infected person doesn't mean AIDS patient)

6- HIV-1 Vs. Immune System

Unfortunately the immune system has failed to kill HIV virus even with its strength and its huge capability of killing other infection, and that's because of:

1- **Nature of the virus**; the virus has the capability to integrate its genome in the cells' genome by integrase enzyme. By this case the virus will hide away from the B cells and cytotoxic T-cells, and they will no longer see it. And this is what calledimmune evasion.

2- The presence of **Reverse transcriptase, RT** which is highly error-prone, so these errors are in the advantage of the virus. Why? Because it will produce new peptides every while and then, so the immune system will not recognize this new peptide. And at the time the immune system will recognize that peptide, a newer peptide would have emerged. The virus is always one step ahead the immune system.
(Normally our polymerase does mistakes but we have sets of enzymes to correct those mistakes (proofreading enzymes). So after the replication and the proofreading the mistakes rate is reduced to very low levels. With the reduced mutation rate, cancer rate is reduced, that's why cancer is a disease of aging.)

3- HIV virus targets**CD4+ cells**, which are very crucial to the function of almost every single cell in the immune system. Once the number of CD4+ cells has dropped, the whole immune system is paralyzed!
It's important to note that CD4 does not present only on helper T cells, but also could be found on Macrophages, Monocytes and Dendretic cells! So all these cells that express CD4can be targeted by HIV. And for that reason some strains are called M-tropic (they attack macrophages) and others are called T-tropic (they attack T helper cells).
** Note: Don't forget the two-key-system (we need the receptor and co-receptor such as chemokines)*

4- The virus **uses the normal trafficking system**; it enters the DC and macrophages in tissue and uses them as transporters to go to the lymph nodes. This is the Trojan Horse Theory.

7- Treatment

If the patient is untreated, death occurs withinmore or less 10 years. But the combined therapy, highly active anti-retroviral therapy (HAART) is very effective in prolonging the patient's life span.HAART is a combined therapy*, taken as a bill and it's very effective in bringing down HIV titer. But at the same time, it has so many side effects, for example, cognitive disorders, increase the risk of many types of cancers, kidney failure and diseases in the heart, liver and bone. Moreover, these drugs are very expensive.

**combined therapy: means more than one drug and each drug has different action are combined, these actions could be one of the following:*

- ***Nucleoside reverse transcriptase inhibitors, NRTIs**: these are nucleoside analogs that cause chain termination.*
- ***Non-nucleoside reverse transcriptase inhibitors, NNRTIs**: these drugs bind allosterically to the RT itself without being a nucleoside analog.*
- ***Protease Inhibitors, PIs**:they block the protease and prevent it from doing its function in transferring the immature virus into mature infectious one (It blocks the cleavage of the long polypeptide that is encoded by the GAG genes, GAG genes encode proteins that are part of a general architecture for retrovirus such as the matrix, capsid and nucleocapsid, this GAG region is translated as a single polypeptide that needs to be cleaved to function well.)*
- ***Integrase Inhibitors, IIs**:they inhibit the integration of the viral genome in the host cell's genome.*

Elite controllers:are patients who are infected with HIVbut they take very long time to show symptoms. Genetics, MHC molecules and other complex combined reasons could all play a role in making one's immune system is better in fighting HIV than others! These are some possible reasons:

1- Their immune system is fighting better and stronger towards the infection so they produce more type 1 Interferon (anti-viral response)
2- Their MHC response is more variable; remember that the one who has high MHC polymorphism can surviveHIV infection more.
3- Their MHC molecules have better ability of presenting HIV peptides to immune system
4- Their cytotoxic T cells are more aggressive in fighting virally infected cells by having special mechanisms, for example, they may be able to mobilize moreGranzyme-B and deliver it to the target cell more efficiently. Or maybe they have a specific polymorphism that lead to increase production of Granzyme-B.

**Note: elite controllers are not the same as the patient who don't have the receptor from the first place, as the later ones are not infected at all!*

8- AIDS in mother and child

HIV can pass from the positive mother to her baby in 25% of cases during:

1- Pregnancy: HIV can cross placenta and cause the disease, and 1 in every 4 affected pregnant will have a positive HIV child. That's why the treatment of the pregnant lady is crucial and the follow-up treatment for the baby for 4-6 weeks is also important in reducing his risk of becoming HIV positive individual!

2- Child birth: those patients should undergo C-section not normal delivery as the titer of the virus in the vaginal sexual fluid and canal is very high! C-section is much safer and cleaner but it's still a risk!

3- Breast feeding: HIV can be transmitted through colostrum "milk"so these patients are advised not to breast feed their babies.

9- Lab tests for HIV (orderedfrom the oldest and leastsensitive to the currently used and more sensitive)

1- HIV-1 or HIV-2 Antibody test: it's pure serology, and it detects the presence of antibodies against viral membrane component. This test is not used nowadays, its window of detection is high as it needs at least 3 months to be able to detect the Abs in the serum.
" an extra information: the window of detection(diagnostic window) is the time needed for a special marker or the tested molecule to appear positive"

2- HIV-1 and HIV-2 Antigen Antibodiescombo test: It's more sensitive and specific and it has a shorter diagnostic window (95% of cases show positive test in the 1st month of exposure and the rest 5% stay up to 3 months). In this test we search for antibodies towards HIV-1 or HIV-2 or the presence of p24 antigen from the virus or both.

3- PCR, it has very short diagnostic window (10-14 daysup to 3 weeks) and may be less and it is a very sensitive test. In PCR we don't look at serology, we look for the presence of RNA or DNA of this virus in the blood, fortunately, few viruses are enough to be amplified and detected by PCR.

***For established cases, following up is important and if the patient reaches a specific level he will be named as AIDS patient and will undergo treatment, follow-up is usually done by:

1- Flow Cytometry by measuring CD4+ cell count and PCR.
(PCR is also could be used hepatitis B monitoring.)
2- CD4/CD8 ratio
we have CD4+ cells in our body more than CD8+. So normally this ratio is more than 1, but in AIDS patient it's less than 1.

A final note from the doctor:

In Jordan, every HIV case must be recorded with the person identity. This has advantages and disadvantages but in that way we are losing cases "as they don't want to be identified". So some people ask for CD4/CD8 ratio (not directly HIV test) but they must have known that CD4/CD8ratio needs very long time to decrease, and it will be too late for them!
Also there is a hot-line for HIV, anyone can ask for information and report cases. And any non-Jordanian case detected here in Jordan will be sent to their original country while the Jordanian ones are treated for free.

Great things never came from comfort zones
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