Pathology

Sheet Slide

number

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بالتوفيق جميعاً لكل من يقرأ.. ولكن أردت إعلامكم أن التفريغ الأول لكل من محاضرة دكتور غسان ومحاضرة دكتور محمد مختلفة المحتوى وبعيدة الترابط لذلك كان علينا أن نجمع التفريغين في ملف واحد كما لو كلٌ بمفرده.

The scientific study of disease including:

1. Patterns 2. Causes 3. mechanism and effect of disease.

We need to know how the disease began, the patterns of the disease, its causes and mechanism. What are its effects on the patient, how it developed and how it happened? Is it possible that the disease might affect the brain or lungs? Given .the reasons and its impact on the body

Pathology isn't only looking under the microscope and having basic disease knowledge. Medical knowledge must also be available. When studying a sample, it is also important to know the age and sex of the patient, and the organ from which the sample was taken.

Examples:

1. **<u>Granuloma</u>**

Granuloma is an organized collection of macrophages (aggregates of histiocytes). Histiocytes are monocytes inside the tissue. Histiocytes cluster up and enter a tissue which in return causes Granuloma. When histiocytes cluster up all the nuclei are joined together in one cytoplasm, the resulted cell is called a multinucleated giant cell. When looking under the microscope we see necrosis in the middle. Necrosis is defined as the death of the tissue in some cases due to bacteria. One special type of necrosis is called Caseous Necrosis which is only complementary with tuberculosis. A special stain is used to diagnose it which is called Fast Acid (Ziehl-Neelsen stain).

2. **Sarcoidosis**

Which is an immunological disease with no known cause (Unknown etiology).

- Expression of discomfort due to structural or functional abnormalities
  The disease could be structural or functional or both.

**** Examples of structural diseases:**
The presence of a mass in the breast. Functionally the patient can breast feed in case she is a mother, but structurally a lump is present in the breast.

**** Examples of functional diseases:**
Hashimoto's thyroiditis which is the chronic inflammation of the thyroid gland. Morphologically the gland looks free of disease, but functionally the inflammation causes hypothyroidism, which results in the underproduction of sufficient hormones by the gland.

****Classification of Diseases:**

1. **Physical/ Mental**

2. **Acute/ chronic**
   Acute: Short, days to weeks
   Chronic: long, months to years
   Sub-acute: is used to describe a disease, whose duration lies between acute and chronic (not used much).

3. **Congenital/ Acquired**
   Congenital: patient was born with the disease (example: undescended testicles)
   Acquired: any disease gained after birth.

4. **Genetic/ Environmental**
   Examples: Hiroshima and Nagasaki bombings, the Chernobyl disaster

5. **Mild/ Moderate/ Severe**
   The doctor can estimate the severity of the disease based on what the patient informs him, for example if the patient is diagnosed with a headache and didn't take any painkillers and the pain decreased alone or because the patient drank lemon it is said to be mild. If the patient took painkillers and the pain decreased it is said to be moderate and if the patient took pain killers, but the pain didn't decrease at all it is said to be severe.

6. **Inflammatory/ Neoplastic/ Degenerative**
   Inflammatory: any disease caused by a viral or bacterial inflammation.
   Neoplastic disease: Any tumor, whether it was malignant or benign.
   Degenerative disease:
   Examples: Gastritis can occur in the stomach but also a tumor might be present. A disease might not be caused an infection nor a tumor, a disease might be caused by drinking chloride for example, which causes gastric erosion. Or it might be that elderly people suffer from knee pain which comes with aging due to rupturing of membranes and cartilages caused by excessive movement. Another example of degenerative diseases is spinal disc herniation.

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** Aspects of disease process:

7. **Epidemiology:**
   Which is not only to study the prevalence of a certain disease, but might also be to study for example the distention differences in goiter disease in a certain country.

1. **Etiology:**
   Cause of the disease, where did it come from, it might be bacterial, viral, fungal, genetic, tumor etc.
   In some tumor cases health professionals look for the cause, for example if it was related to a certain virus

2. **Pathogenesis:**
   Path: the path/ Genesis: formation of the disease, from where (how did the disease enter the body)

What are the events that happened in the body from the moment the bacteria entered the body, and the development of the disease?
Etiology explains the causation, as pathogenesis is concerned with the transmission of the disease and its development.

3. **Morphological changes:**
   Example: A dislocated swollen bone.
   The morphology is the presence of a legend (a disorder called legend), there's an injury in the middle, beginning or end of the femur.
   Morphology is concerned with the shape for example if there is swelling or redness around the injury. When we diagnose a tumor we have to perform a morphology test. Example: A brown mold on the face, patient noticed it 4 years ago, its shape didn't change and it didn't affect the patient.

4. **Clinical significance:**
   How the disease affected the patient clinically, for example if he couldn't eat or walk anymore due to the disease. (Effect of disease on the patient).
   If the patient has a mouth infection and he couldn't eat any more (loss of appetite)
   A patient presented with appendicitis, which caused loss of appetite due to excessive vomiting.

5. **Diagnosis:**
   We can diagnose clinically, by radiology or laboratory.
   A patient presented with dysfunction of the stomach, stomach irritation when eating and high acidity of the stomach, the blood test diagnosed the patient with a type of bacteria. (Blood test are laboratory). Radiologically we can use ultrasound to diagnose.
   After diagnosis comes management of the disease, which is how we're going to treat the patient. If it was caused by a bacteria we'll give the patient an antibacterial treatment, if it was an ulcer we'll treat the patient accordingly.
   If we suspect a tumor if it's benign we remove it, if it's malignant we'd have to perform a gastrectomy.
   Complications of the disease, for example in the case of appendicitis as the appendix might rupture and cause allergic reactions. We didn't

mention drug complication because we're only dealing with complications of the disease.

6. **Prognosis:**
   Future of the patient, whether it was a good or bad prognosis.
   Examples: A kid has an abnormal bone in his leg, we removed it → Good prognosis
   A cancerous tumor in the bones that might reoccur and cause amputation → Bad prognosis
   A cancerous tumor that reached the lungs → Bad prognosis (Because the case arrived in a developed phase)
   A female presented with a uterine tumor that reached the lungs which means it reached a very developed phase → Bad prognosis
   Woman pre presented with uterine cancer in early stages we perform a hysterectomy → Good prognosis (whether it was before the treatment or after, because the tumor wasn't spread all over the body)

7. **Prevention:**
   Immunological disease caused by the immune system (rheumatism)

8. **Risk factors:**
   Any person allergic to peaches, peach is a risk factor
   It is relevant to the disease

- Red blue liver is liver cirrhosis
- Symptoms: what the patient tells me
- Signs: what I see as a doctor (Presentation)
  For example if I see swelling and a mass the patient didn't inform me about.
- Some people live with diseases and die with them but not because of them.

Cell injury

Apoptosis: programmed cell death, it is programmed in the genetic apparatus of the cell.
If the cell doesn't die in the exact day another cell will be produced in the same place and this called a tumor.
Note: delay of apoptosis is one of the mechanisms of the tumor or cancer.

Our cells are divided into 3 types:

1. Continuously dividing cells: which live for a short period of time (18-24hour)
   Ex: intestinal epithelial cells live for (3-7days)

2. Stable cells: they have the ability to divide but they cannot work unless they are exposed to certain agent
   Ex: liver cells

3. Non-dividing cells: Ex: nerve cells and cardiac cells
   If they get injured they will be replaced by a substitute tissue (connective tissue).

   Every cell has a life standard (the time that a cell lives until it dies and it gets replaced by another cell, in the same place and the same type)

- **Factors causing cell injury:**

1. **Physical agents**: Ex: trauma
2. **Chemical agents:** cigarette smoking, alcohol
3. **Infectious agents:** bacteria, viruses, parasite
4. **Immunological reactions:** antigen-antibody reaction
   It will be:

a. Good Example: to understand the presence of infection
   Ex: bee pinch
b. Bad Example:
   1. anaphylactic reactions: exposing mast cells may lead to anaphylactic shock
   2. autoimmune diseases: occurs when the immune system attacks the body

5. **nutritional agents:** like: obesity, protein deficiency
6. **genetic defects:** genes are what balance between health and disease
7. **oxygen deprivation:** the most common cause of cell injury
   Hypoxia: oxygen deficiency (important cause of cell injury)

- Who is hypoxic patient?
    1. People who live in high places
    2. People have lung problems
    3. People have Anemia
    4. People who have closure in their blood supply (both arterial and venous)

Note: If you have ischemia you have hypoxia, but the opposite is not true (ischemia is one cause of hypoxia)

- Ischemia: is a condition in which the blood flow (and thus oxygen) is restricted or reduced in a part of the body.
  And it is the most common cause of cell injury
- Aging: age changes that occur to the cell, and is generally defined as the progressive decline in the resistance to stress and other **cellular** damages, causing a gradual loss of **cellular** functions and resulting eventually in **cell** death.
- If the cell doesn't expose to one of the 7 factors, it will enter in cell aging
  Aging:
  Undifferentiated cell → young differentiated cell → old → very old
  Apoptosis
- Apoptosis Occurs every day to millions of cells in our body

- Cellular aging mechanism:

1. Intrinsic:(genetic factors)
   Cell Genes are programmed to stop working in the exact day, the repair process also stopped and abnormal signals will appear
2. Extrinsic:(environmental factors)

So reduction of chromosomal activity occurs, the cell tries to retain to the normal state by activation by itself, no response occurs so the cell will die.
Ex:
In the skin there are accumulation of cells in layers , cells on the upper part are exposed to environmental factors more than lower cells ,when they get exposed to environmental factors the genes stop the repair of DNA and they get replaced by another cells

- When cells get injured, structural and functional (occur first)changes occur

- Unstressed cells are exposed to stress so they try to resist, making adaptations, if the cell fails to resist ,it will enter the reversible cell injury state

- Reversible cell injury(RCI) properties:

1. Drop in function
2. No structural changes
3. If the stimuli stops the cell retains normal (because of that it's called reversible)

- If the stress continues the cell enters the irreversible cell injury state , at this point if we stop the stress, the cell won't go back to its normal state because it's too late
- Note for the chart in page14: the function decrease as duration increase

- The level of structural changes:

1. Biochemical
2. Ultra-structural (mean the organelles)
3. Microscopic appearance of the cell
4. Gross morphologic changes (macroscopic structure)

Note: these changes occur together when cells tend to die

- The cellular response to injury depends on:

1. Type: physical is different from chemical
2. Duration: as the duration increases the effects of injury also increase
3. Severity: if the number of cells, large or small, if the area is large or small

- The main targets of injury are:

1. Cell membrane integrity
2. ATP generation
3. Protein synthesis
4. The integrity of the genetic apparatus

- How does the mechanism occur?

1. Loss of membrane integrity (effects on the entrance of ions and particles to the cell)
2. ATP depletion and mitochondrial damage
3. Increased intracellular calcium
   Explanation: calcium is present in and out of the cell in a balanced state due to the presence of a membrane.
   Calcium is present inside the cell in two places:
   - Cytoplasm
   - Mitochondria and endoplasmic reticulum
     When the membrane loses his integrity, calcium enters the cell with water (influx of H2O)
     The first sign that indicates cell injury under the light microscope is cell swelling, so the synthesis of proteins decrease.

4. free radical-induced injury
5. Protein breakdown: the damage of cytoskeleton is the most important because the shape of the cell will be lost.
6. DNA damage

The increase of calcium inside the cell activates four enzymes:

1. Protease: destroys the cytoskeleton and membrane
2. ATPase: reduce ATP
3. Endonuclease: nucleus chromatin damage
4. Phospholipase: breakdown phospholipids and gives off cell product (membrane damage)

- Summarization
  A Defect in membrane integrity causes influx of calcium with water and efflux of potassium, cell swelling, increase cytosolic calcium and activates the four enzymes

- Mitochondrial damage and ATP depletion:
  The structure of mitochondria has pores which contains granules
- Mitochondrial dysfunction in cell injury:
  When cell swelling occurs, the pores of mitochondria become larger, the granules (cytochrome c) go out to the cytoplasm and go to other proteins and cause apoptosis

Microscopic features of the cell injury:

1. Cell swelling
2. Fat deposition

Free radicals

Definition: unstable chemical species with single unpaired electron in the outer orbital
Ex: nitrate, reactive oxygen, H2O2

What are the sources of these substances?
From radiation, chemicals, bacteria, etc.
How can the body counter them?

By using antioxidants (they block the formation of free radicals or stop their effect)
One example of antioxidants is omega3

- Antioxidants activity:

1. Endogenous
2. Exogenous

- Chemical injury mechanism:

1. Direct: we use a toxic chemical substance to the cell (the cell has a receptor to this substance so it will enter the cell, and get stored there)
   Ex: Hgcl2 poisoning

   The cell has a receptor to Hgcl2 in the membrane → inhibition of ATPase increase membrane permeability → influx of Ca and water → cell swelling and death
2. Indirect: the component isn't active or toxic, but if it enters the cell ,it becomes active and will be metabolized
   Ex: CCL4
   When it enters the cell it will be metabolized and changed into the toxic CCL3 by the liver.

Note: the effect of both direct and indirect is:
1. Increase permeability of Ca and water so damage the membrane
2. Cell death
Cellular adaptation to injury:
If the cell is exposed to stress, it tries to adapt
Is adaptation a good state?
No but it's better than what comes next
The continuity of stress forces the cell to enter the irreversible cell injury state

- physiological adaptation: occur normally and if they don't
- happen a disease will occur

Ex:
During pregnancy uterine cells increase in size (hypertrophy) and number (hyperplasia) because of hormones
After pregnancy the effect fades and cells tend to retain to their normal condition by apoptosis
Note: some cells undergo hypertrophy and others undergo hyperplasia or both

- Pathological adaptation:
  Ex: hormones produced by a tumor

****Mechanism of cell adaptation :**

- Up-down regulation of receptors
- Receptor binding
- Increase or decrease of protein synthesis
- Switch from producing one type of protein to another

Types of adaptive responses:

1. Atrophy: decrease in cell size by decreasing protein and cell substance synthesis but have the same shape
2. Hypertrophy: Increase in cell size
   Ex: in cardiac cells hypertrophy occurs because it's a non-dividing cell
3. Hyperplasia
4. Metaplasia: change from one form to another
   Ex: what happens with smokers.
5. Dysplasia: disordered
6. Hypoplasia

Nature of Injurious Stimulus	Cellular Response
Altered physiologic stimuli; some nonlethal injurious stimuli	Cellular adaptations
Increased demand, increased stimulation (e.g., by growth factors, hormones)	Hyperplasia, hypertrophy
Decreased nutrients, decreased stimulation	Atrophy
Chronic irritation (physical or chemical)	Metaplasia
Reduced oxygen supply; chemical injury; microbial infection	Cell injury
Acute and transient	Acute reversible injury Cellular swelling fatty change
Progressive and severe (including DNA damage)	Irreversible injury → cell death Necrosis Apoptosis
Metabolic alterations, genetic or acquired; chronic injury	Intracellular accumulations; calcification
Cumulative sublethal injury over long life span	Cellular aging