Cystic Fibrosis (CF)

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عشان هيك في كتير دراسات عليه و في foundations خاصة لعلاج مرضى الـ CF ، و بشكل عام معروف كتير عن هاد المرض

- Among the most common life shortening genetic illnesses, median survival is ~~41~~ 47 years
- Chronic, progressive obstructive lung disease.
- Associated with pancreatic insufficiency, liver disease, CF related diabetes militus.
- There is no currently no cure for CF

Epidemiology

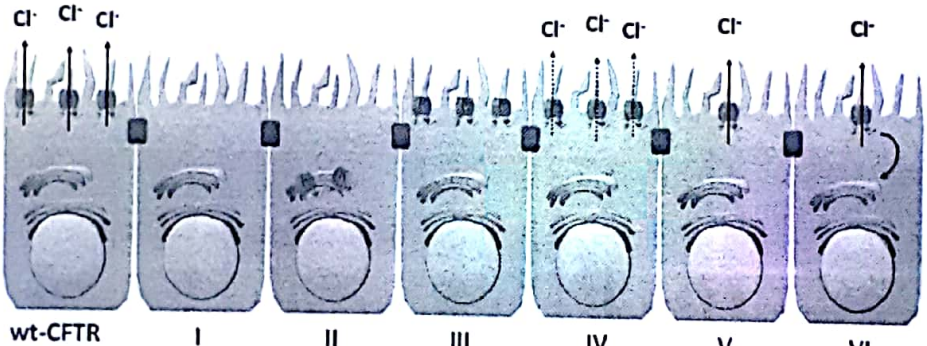
- 30,000cases in North America.
- Incidence 1:3200 in whites, 1:15000 in people of african decent. → More common in whites (caucasians)
- Incidence of CF in Jordan ؟؟؟
  ↳ In Jordan we have about 200-250 cases
  * In Jordan we have a problem in diagnosing CF So a lot of cases are misdiagnosed

Pathogenesis

- The disease is caused by a genetic mutation on chromosome 7q31.2, which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein.
  ↱ This protein is present on cells other than epithelial cells, but in CF the main problem is with those on epithelial cells.
- CFTR is an apical epithelial chloride channel.
- 1900 mutations have been identified, all categorized into 6 distinct classes.

* منش مهم نحفظهم

- Class 1: Lack of protein production
  → The most common mutation
- Class 2: Defect in protein trafficking with degradation in endoplasmic reticulum → apical membrane ما بطلع عل
- Class 3:Defective regulation of CFTR
- Class 4: Reduced chloride transport through the apical membrane
- Class 5: Splicing defect with reduced production of CFTR
- Class 6: Decreased CFTR stability
  بطلع و بعدين يرجع و بصيرله degredation



Most Common

These are associated w/ a better prognosis

هاد النوع من ال mutation اله دوا ، بس الحالات اللي من هاد النوع قلال.

* صار مهم نعرف نوع ال mutation اللي عند المريض ، لأنه صار في medications معينة حسب ال mutation

- Most common mutation delta 508, it is a class 2 mutation, [70% have one gene, 50% have 2 genes.] → من كل مرضى الـ CF
- G551D is a class 3 mutation, that is targeted by Ivacaftor.

- 2 mutations are needed for the disease
- Classes 1-3 are associated with early onset of disease, and pancreatic insufficiency ✡
- Classes 4-5, are associated with later onset lung disease, and pancreatic sufficiency. ✡

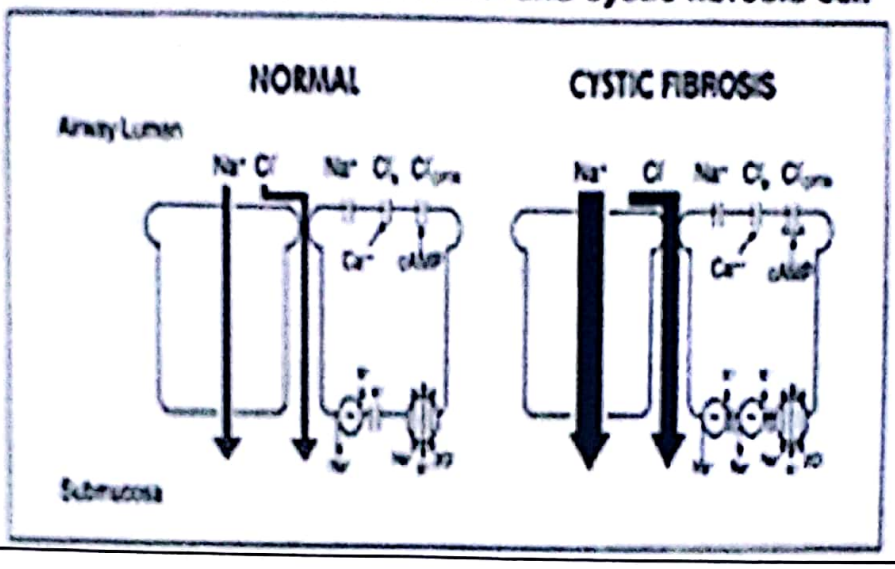
* مهم نعرف إنه معظم مرضى الـ CF عندهم Pancreatic Insufficiency

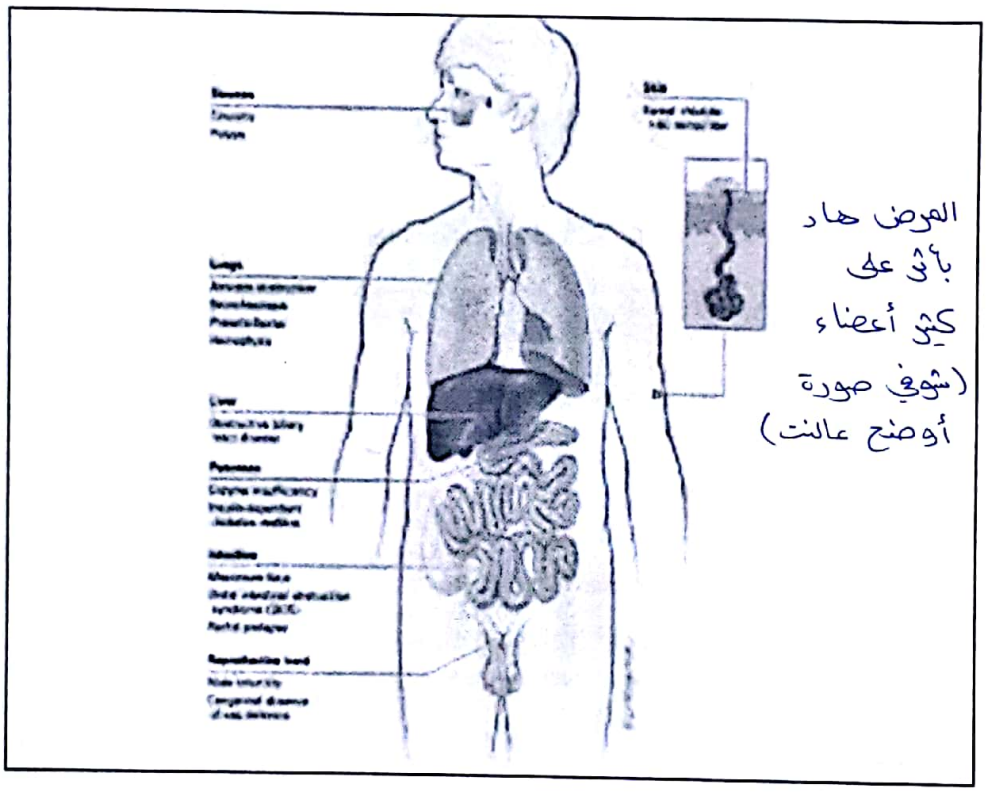
* about 15-20% have pancreatic sufficiency

* بشكل عام الـ CF معظم كيسز عنا بالأردن ، بس كيسز بدخل بالـ DDx

CFTR: A cAMP-Regulated Chloride Channel

The net ion flow across normal and cystic fibrosis cell





المرض هاد
بأثر على
كتير أعضاء
(شوفي صورة
أوضح عالنت)

Pathophysiology

- Lungs: Mucus plugging==inflammation, chronic infection, small airway obstruction, bronchiectasis
- Exocrine pancreas, intestines and liver: vicid secretions==Pancreatic insufficiency, intestinal obstruction,cholestasis.
- Other systems: Pansinusitis, nasal polyps and infertility, increased salt excretion in the sweat.

Cystic fibrosis → differential Dx بالـ بدخل كيتي

Diagnosis

- Cyctic Fibrosis Foundation diagnostic criteria:
  - The presence of 1 or more phenotypic symptoms of CF like, recurrent sinopulmonary disease, nutritional of gastrointestinal symptoms, or absence of vas deference.
  - OR
  - Positive family history of CF in a sibling
  - OR
  - Positive newborn screen, → It is found that early detection and management of the disease can ↑ the life expectancy of the pts.
    - with evidence of chloride transport abnormalitis
      - Abnormal sweat test on 2 separate occasions
      - Abnormal nasal epithelial cell potential
      - The presence of 2 known CF causing mutations on genetic testing

* ملاحظة * بشكل عام عشان أعمل screening لأي مرض لازم أكون بقدر أعمل اشي (أعالجه) أو أستفيد من فكرة اني اكتشفته (يكون preventable)

→ Newborn screening includes
- Hypothyroidism
- Phenylketonuria
- galactosemia

* The sweat test measures the concentration of Cloride that is excreted in sweat. It is used to screen for CF.
Due to defective chloride channels (CFTR), the concentration of the Cl^- in sweat is elevated in individuals w/ CF

The gold standard for diagnosis of CF remains the pilocarpine iontophoresis sweat test developed by Gibson and Cooke in 1959

هاد التست قديم و صعب بيعمل (خوّاته كيوة)

Interpretation of Sweat Chloride Concentration	
Group	Interpretation
Infants age 0–6 months	
Sweat chloride concentration (mEq/L)	
0–29	CF is unlikely
30–59	Intermediate
→ 60	Indicative of CF
Infants age >6 months, children, and adults	
Sweat chloride concentration (mEq/L)	
0–39	CF is unlikely
40–59	Intermediate
→ 60	Indicative of CF

>60 CF عنو

Note: Read about the method of how this test is done on Wikipedia.

المشكلة بالأردن انه هاد التست نتائجه مش دقيقة لأنه ما بطلعوا chloride level اد بطلعوا اد NaCl .

Diagnosis

- False positive sweat Cl:
  - Eczema, Ectodermal dysplasia, malnutrition, congenital adrenal hyperplasia, Adrenal insufficiency, hypothyroidism.
- False negative sweat Cl:
  - Dilution, edema, inadequate sweat.

Diagnosis

- Abnormal nasal potential difference measurement. (Absence of voltage after pilocarpine administration).
- Fecal elastase to measure exocrine pancreatic junction.
  To determine if there is
  ↳ Pancreatic sufficiency
  ↳ Pancreatic insufficiency
- Genetic testing:
  - usually look for 30-96 mutations.
  - Complete sequencing of the CFTR gene is available for atypical cases
  - List of clinical manifestations associated with the individual CFTR mutations are available on www.cftr2.org

هاد البنت
مرض جيد بس
مش موجود بالكويت

Diagnosis

- Newborn screening was implemented in all states in 2010
- Newborn screening was associated with improved nutritional status, and lung function at age 6.
- It has 90% sensitivity but low specificity.
- Immunoreactive trypsinogen is measured in the newborns blood.
  - a positive test needs referral to a pulmonologist , and the performance of a sweat test.
  - False negative newborn screening can happen especially in infants with meconium ileus.

Clinical Manifestations

- Recurrent sinopulmonary infection
- Stetorrhea (due to malabsorption)
- Failure to thrive.(The triad of symptoms)

و بعدين بيحتاجوا lung transplant

Respiratory failure و bronchiectasis بسبب الالتهابات المتكررة

Clinical Manifestions by age

- Hyperechoic bowel of fetal US, is suggestive of CF
- Delayed meconium passage, meconium plugging and meconium ileus, are present in 15-20% of infants with CF.
  - Due to high protein in meconium
  - inspissation of meconium is bowel leading to intestinal obstruction…usually needs surgical removal
- Rectal prolapse
  - Seen in patients 6m—3years
  - Due to malnutrition, elimination of large stools

فأي طفل بعمر عندو هيك مشاكل screening for CF

Clinical Manifestions

- Less frequent manifestations in infancy
  - Salt depletion sydrome, results in hyponatremic, hypokalemic, hypochloremic metablolic alkalosis.
  - Prologed neonatal jaundice from intrahepatic biliary stasis, and extra hepatic biliary obstruction.
  - Edema and hypoprotinemia from malabsorbtion
  - Hemorrhagic disease of the newborn from Vit K deficiency.

(In general CF pts have deficeincy in fat absorbable vitamins)

↳ A/K/E/D

Clinical Manifestations

- In older children, adolescents and adults.
  - Recurrent lung infection
  - Poorly controlled asthma
  - Bronchiectasis
  - Recurrent sinusitis and nasal polyps
  - Hemoptysis, pneumothorax
  - Respiratory failure

Clinical Manifestations

- Malabsorption
- DIOS…Distal Intestinal obstruction syndrome
- Rectal prolapse
- Liver disease
- Infertility absent vas deference

Management

- The aim of management is to
  - Maintain optimal lung function
    - Antibiotics
    - Lung clearance
    - Anti inflammatory medications
  - Maintain optimal nutritional status

المفروض مرضى الـ CF يكون الـ centers خاصة فريق يتعالجوا فيها (مش بالعيادات و المستشفيات العادية) حتى يحصل على الرعاية الكويسة اللي محتاجها من ناس متخصصة بهاد الموضوع

Management

- In the US cystic fibrosis care is provided at CF foundation accredited centers with a multi disciplinary team approach.

Cystic Fibrosis Foundation's Pulmonary Clinical Practice Guidelines Committee developed recommendations that were based on a systematic review of the literature and assessment of the available evidence based on an established grading scale. These guidelines were updated in 2013

ما تدققي كتير عليهم

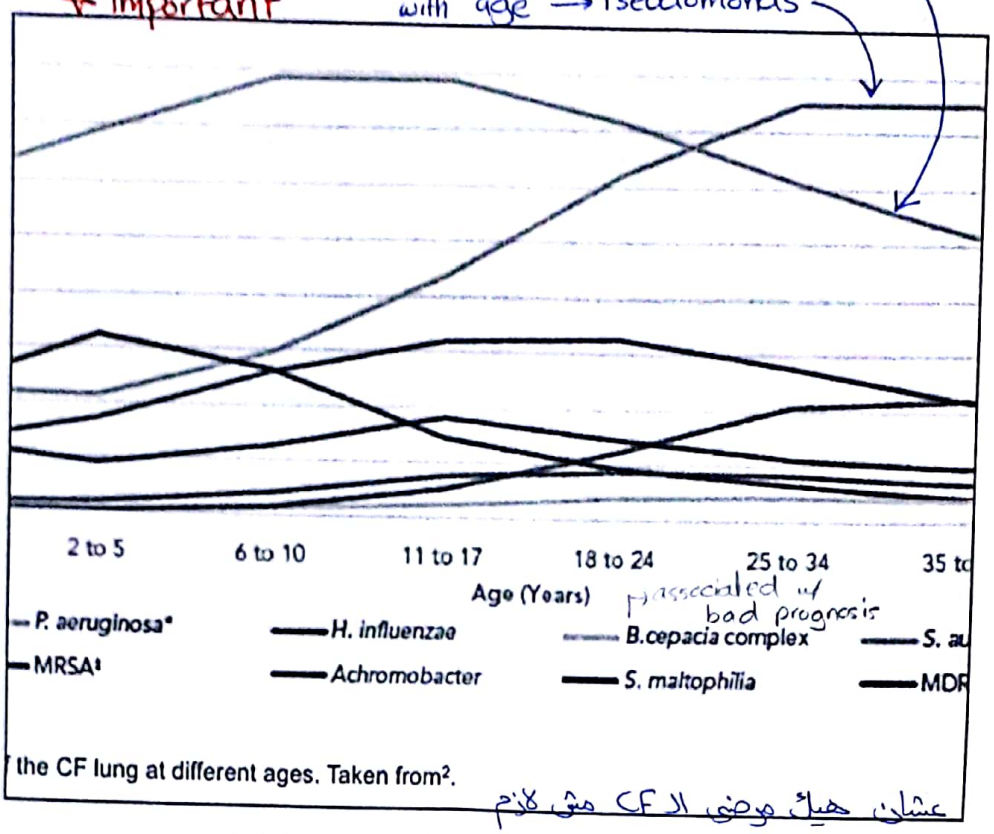
Management

- Chronic airway infection
  - surveillance cultures; pseudomonas, staph aureus, atypical mycobacterial infections, fungal infections
  - First evidence of pseudomona colonization is usually treated with inhaled tobramycin
  - Patients with chronic pseudomonas infection, can benefit from inhaled antibiotics every other month
  - Acute exacerbations are treated with IV antibiotics usually double coverage for pseudomonas and depending on the sensitivities obtained by sputum culture.

CF pts in childhood → The most common bacteria is Staph aureus

*Important

with age → Pseudomonas



associated w/ bad progress

the CF lung at different ages. Taken from[2].

عشان هيك مرضى الـ CF مش لازم

يتحطوا مع بعض ، كل واحد لازم يعزلوا و يعالجوا لحاله

عشان ما يعدوا بعض

Management

- Airway clearance
  - Percussion, postural drainage, active cycle breathing, positive expiratory pressure, high frequency chest wall oscillation.
  - Usually combined with mucus alternating agents like DNase, and hypertonic saline 7%

مش موجودين بالأردن

  - Usually done twice daily and increased frequency with acute infections.

* ما تدفقي كثير عالـ management
بس الـ Dx و الـ organisms مهمين

Management

- Disease-Modifying Therapies
  - Ivacaftor is an oral pharmacologic potentiator
  - Activates defective CFTR in patients with class 3 mutation G511D
  - Approved for patients with at least one G511D mutation

Management

- Chronic airway infammation
  - Ibuprofen: high doses (blood levels of 50-100microgm/ml) have been associated with decrease neutrophil migration and decreased inflammation
  - Azithromycin: used 3 times/week, improves lung function and lessens exacerbations
  - Sterids: Should not be used routinly

Management

- Pancreatic enzyme replacement therapy
  - Pancreatic enzymes must be taken with every meal and snack
  - The dose is 2000-2500u/kg of lipase/meal
  - Too high of a dose causes fibrosing colonopathy
- Fat soluble vitamines replacement therapy
  - AKED vitamines

Management

- Management of the compilcations
  - Pulmonary exacerbation: worsening cough, shortness of breath, fatigue or weight loss, decrease in lung functions
  - Treament is with antibiotics, oral,IV or inhaled depending on culture results and sensitivities.

Management

- Hemoptysis 9% of patients:
  - usually from bronchial arteries, in advance disease
  - treatment is antibiotics for mild to moderate, 5-250ml
  - Bronchial artery embolization or lung resection for sever bleeding
- Pneumothorax in 3.4% of patients
  - If small to moderate management depends on degree of respiratory compromise
  - If large a chest tube needs to be inserted
  - if large and recurrent, chemical or surgical pleurodesis

Management

- Chronic rhinosinusitis and nasal polyps
  - Medical therapy with inhaled steroids, saline rinses
  - surgery, functional endoscopic sinus surgery.
- DIOS
  - Vicid fecal matter obstructing distal intestines, risk factors include fat malabsorption secondary to insufficient enzyme replacement, dehydration, a history of meconium ileum
  - Treatment is hydration, and osmotic laxatives, in cases of complete obstruction gastrografin enema

Management

- CF liver disease
  - Patient get biliary fibrosis that leads to biliary cirrhosis and liver cirrhosis
  - Hepatomegaly, abnormal liver functions and abnormal liver US and and an abnormal liver biopsy
  - Treatment is ursodeoxycholic acid

Management

- Cystic Fibrosis Related Diabetes Mellitus Type 1
  - CFRD has been associated with decreased body mass index, lung functions and mortality
  - Early control improves outcome and mortality
  - Microvascular complications of DM can happen
  - Incidence increase 5% per year after 10 years of age, and 10% per year after 20 years of age
  - Recommended to perform a glucose tolerace test yearly after 1 year of age, HA1C is not recommended as in underestimates the glycemic load
  - Treatment is with Insulin, oral hypoglycemic agents are not recommended
  - Caloric restriction is not recommended, intake of carbohydrates is not discouraged.

Management

- CFTR modulator therapies
- Ivacaftor
- Ivacaftor and lumacaftor Orkambi

Table 1. Most common CFTR mutations causing CF in 2013

Mutation	Prevalence (%)	
F508del	86.4	Most Common
One copy	39.9	
Two copies	46.5	
G542X	4.6	
G551D	4.4	

Abbreviations used: CFTR, cystic fibrosis transmembrane conductance regulator; CF, cystic fibrosis.

Management

- Lung transplantation
  - 5 year survival about 70%

← عادة الـ lung الجديدة بصير الها colonization بنفس الـ organisms اللي كانت موجودة بالـ lung القديمة و السبب إنه هاي الـ organisms رح تيجي من الـ sinuses

- Questions???