Text Book of Medicine

(For Medical Students and Practitioners)

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Preface

Dear Doctors, Greetings. Practice of Medicine, though difficult, is one of the crucial subject for post graduate, Ph.D. entrance examinations.

This edition of book has been completely revamped and updated. This e-book provided with colour pictures to make understanding of the text, lot easier. This will be quite handy for final year students. It will be adequate for the final year medicine theory examination and at the same time it will orient you, exactly towards entrance examinations so that getting a P.G, Ph.D. of choice immediately after completing internship become a reality!

This text book of medicine is to link recent scientific advances to disease pathogenesis and therapeutic innovations. After studying this book, student will be able to answer all the questions and have a through explanation for each of the answers.

This text book is dedicated to all medical students and practitioners.

We have tried to make this book error free but sincerely apologize for any mistake that may have escaped my notice.

We will highly appreciate the suggestions and criticisms are most welcome from our readers for the improvement of the book.

Dr. Siva Rami Reddy E

Dr. Tanuja B

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Chapter - 1

Diseases of the Cardiology

Ischaemic Heart Disease

Ischemic heart disease also called as coronary heart disease. In the India one in three men and one in four women die from this disease. Chronic coronary artery disease (CAD) is estimated to affect 16.8 million people in the United States; of these, 9.8 million have angina pectoris, and nearly.

8 million have had a myocardial infarction (MI). In 2002, out of 57 million deaths worldwide, approximately 16.7 million were due to cardiovascular disease (as compared with approximately 5 million due to tuberculosis, human immunodeficiency virus, and malaria combined), and 80% of these cardiovascular deaths were in the developing world. The article provides a state-of-the-art review of the literature on cardio vascular diseases for interested medical, dental, ayush physicians; appropriate articles were identified by searching the international journal database for the following terms: cardio vascular disease, causes.

Aetiology

Age and Male Sex: Males are more risk when compared to females. Family history: Family aetiology may be due to genetic factors or the effects of a shared environment (diet, smoking habits etc.). Hyperlipidaemia, hyperfibrinogenemia and abnormalities of other coagulation factors are often geneticallydetermined.

Smoking: Tobacco is probably the most important avoidable cause of coronary disease.

Hypertension: The incidence of coronary artery disease increase as blood pressure rises and excess risk is related to both systolic and diastolic blood pressure.

Hypercholesterolaemia: Patient with familial hyperlipidaemia have a high incidence of premature coronary disease and many epidemiological studies have demonstrated a positive correlation between mean population and plasma cholesterol concentration and morbidity and death from coronarydisease.

Diabetes Mellitus: This is associated with a increased incidence of ischaemic heart disease (IHD) and with a tendency to diffuse coronary atheroma.

Haemostatic factors, physical inactivity, obesity, alcohol, mental stress may leads to ischemic heart disease.

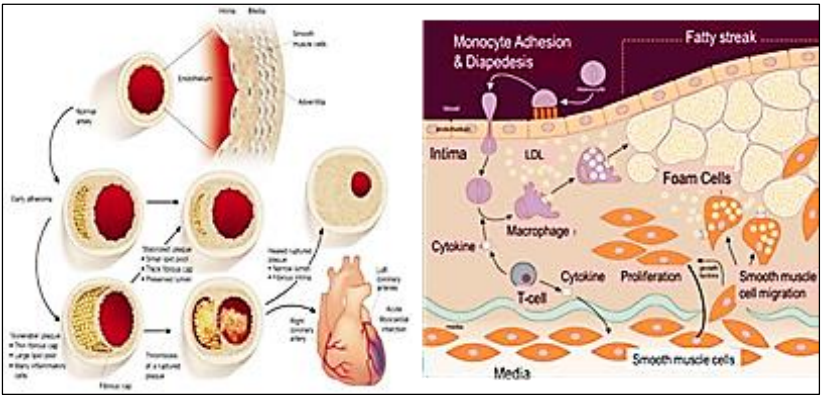


Fig 1: The evolution of an atheromatous plaque

Pathophysiology

Mechanisms that account for a minority of fatal coronary thrombosis include superficial erosion, intraplaque hemorrhage, and the erosion of a calcified nodule. Thus, physical disruption of the atherosclerotic plaque accounts for almost all acute coronary thrombosis. Disrupted plaques provoke thrombosis in several ways. First, contact with collagen in the plaque's extracellular matrix can trigger platelet activation. Second, TF produced by macrophages and SMCs activates the coagulation cascade. The disrupted plaque thereby represents a "solid-state" stimulus to both thrombosis and coagulation; these pathways reinforce each other, as thrombin generation amplifies the activation of platelets and other cells in the lesion. Conversionof fibrinogen to fibrin and release of von Willebrand factor from activated platelets can provide the cross-linking molecular bridges between platelets that yield the dense, 3-dimensional network of platelets entrapped in fibrin characteristic of the "white" arterial thrombus. In addition to the solid state of the disrupted plaque, the "fluid phase" of blood can predispose toward coronary thrombosis. Plasminogen activator inhibitor-1 (PAI-1) extinguishes the body's natural fibrinolytic mechanism that combats the persistence and accumulation of thrombi by inhibiting urokinase-like and tissue-type plasminogen activators. Circulating levels of PAI-1 increase in diabetes and obesity, and mediators of hypertension such as angiotensin II can augment PAI-1 expression by various cell types.

Furthermore, disrupted plaques can elaborate particulate TF, which can heighten the thrombogenicity of blood. These fluid-phase changes led to the concept of the "vulnerable patient," thus augmenting our appreciation of the so called "vulnerable plaque". In the context of ACS, the distal embolization of TF rch debris spewing in to the blood stream from the core of the suddenly disrupted plaque may promote distal thrombosis in the microcirculation. Such distal embolization explains in part the "no- reflow" phenomenon that can complicate both spontaneous and iatrogenic plaque disruption and prevent effective reperfusion of the distal microcirculation.

Coronary heart disease may leads to angina. Angina causes the following feeling across the chest.

Clinical Features: Squeezing, pressure, heaviness, tightening, burning, aching. Angina might also cause the following symptoms: Indigestion, heart burn, weakness, sweating, nausea, cramping.

Diagnosis

ECG may show evidence of previous myocardial infarction. The most convincing ECG evidence of myocardial ischemia is obtained by demonstrating reversible ST segment depression or elevation with or without T wave inversion at the time the patient is experiencing symptoms. Coronary artery calcium scanning with CT is a screening tool that has no role in patients with established CAD in whom the presence of coronary artery calcification is a given. Furthermore, the specificity of the coronary calcium score for obstructive coronary lesions is low. Although CT coronary angiography is showing promise for noninvasive detection of obstructive CAD in major epicardial arteries, it is still limited by a high number of false-positive results (up to 50% with severe calcification and coronarystents), specific patient selection (heart rate must be regular and <70 beats/min; patient must hold breath for 15 seconds), and high dose radiation exposure. Magnetic resonance imaging may be used for stress perfusion or stress wall motion imaging as well as noninvasive coronary angiography. Most heart valve prostheses and vascular stents are compatible with MRI; however, MRI cannot be used in the presence of certain implanted metal objects or medical devices, such as pacemakers or implantable cardioverter defibrillators.

However, electronic rhythm management devices and other cardiovascular devices are being developed that could be compatible with MRI. Exercise tolerance test is usually performed using a standard treadmill or bicycle ergometer protocol to ensure a progressive and reproducible

increase in workload while monitoring the patients ECG, blood pressure and general condition.

Raynaud's Diseases

It is caused by intense vasospasm of peripheral arteries. Raynaud's is a rare disorder that affects the arteries. Arteries are blood vessels that carry blood from your heart to different parts of yourbody.

Causes: Many causes of Reynaud's disease.

Example includes:

- Diseases and conditions that directly damage the arteries or damage the nerves that control the arteries in the hands andfeet
- Repetitive actions that damage the nerves that control the arteriesin the hands andfeet
- Injuries to the hands andfeet
- Exposure to certain chemicals. E.g. beta adrenoceptor,ergotamine and derivatives
- Medicines that narrow the arteries or affect bloodpressure
- Occupational exposure to vibrating tools andcold
- Cryoglobulinemia
- CRESTsyndrome

Fig 2: Raynaud's disease

Clinical Features

- Turn pale or white and thenblue
- Feel numb, cold, orpainful
- Turn red, throb, tingle, burn, or feel numb as blood flow returnsto the affected areas

Diagnosis

Your doctor will look at your fingers and toes to check the health of your skin and nails and to check blood flow to these areas. Cold stimulation test can be used to trigger Raynaud's symptoms. For this test, a small device that measures temperature is taped to your fingers. Your hands are then exposed to cold-they're usually briefly put into ice water. Your hands are then removed from the cold, and the device measures how quickly your fingers return to their normal temperature. If you have Raynaud's, it may take more than 20 minutes for your fingers to return to their normal temperature. Because results of this type of test are not always consistent, your doctor may do other tests to check for Raynaud's.

Pericardial effusion

Collection of fluid in pericardial cavity.

Causes:viral infection, tubercular and non-infective like uraemia, myxedema, neoplastic, myocardial infection.

Clinical Features

Clinical features of pericardial effusion are dry cough, dyspnoea, fever on and off, palpitation, weakness, precordial pain, pain in upper abdomen, giddiness, difficulty in swallowing. Sign of the pericardial effusion are rapid pulse, hypotension, JVP raise, bilateral and pitting type of pedal oedema, peripheral cyanosis presented dyspnoeic.

Diagnosis

Low voltage of QRS complexes in ECG, pear shaped cardiac shadow, transverse cardiac diameter increased, oligaemic lung fields.

Management

Rest and easily digestible, nutritive diet.

Aortic Aneurysm

An aortic aneurysm is an enlargement (dilatation) of the aorta to greater than 1.5 times normal size. They usually cause no symptoms except when ruptured. Occasionally, there may be abdominal, back, or leg pain.

Causes

Atheromatous disease-affects ascending or descending aorta, aortitis and collagen vascular diseases-affect thoracic aorta: cystic medial necrosis, marfan's syndrome, ehlers-danlos syndrome.

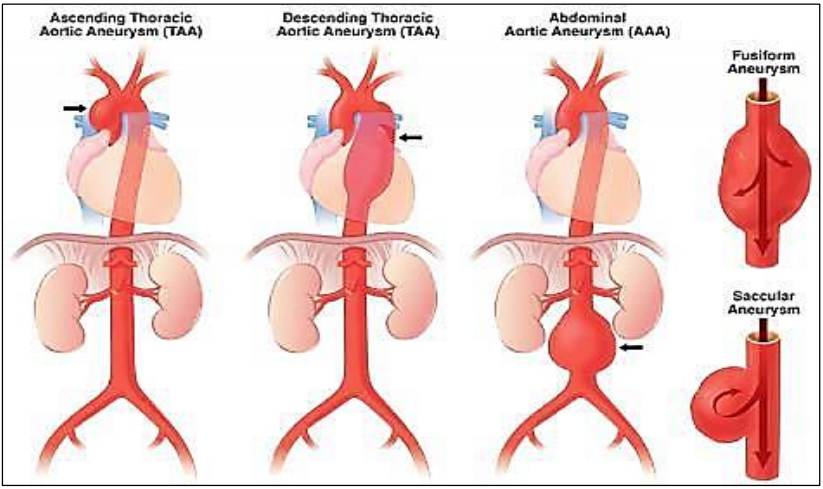


Fig 3: Aortic aneurysm

Clinical Features

Most intact aortic aneurysms do not produce symptoms. As they enlarge, symptoms such as abdominal pain and back pain may develop. Compression of nerve roots may cause leg pain or numbness. Untreated, aneurysms tend to become progressively larger, although the rate of enlargement is unpredictable for any individual.

Rarely, clotted blood which lines most aortic aneurysms can break off and result in an embolus. Aneurysms can be found on physical examination. Medical imaging is necessary to confirm the diagnosis and to determine the anatomic extent of the aneurysm. Signs are aneurysm may be palpable in abdominal aorta, evidence of widespread vascular disease, stigmata of distal embolisation, haemodynamic collapse (hypotension, tachycardia, shock), with rupture of aneurysm.

Management

Emergency surgery.

Rheumatic Heart Disease

Rheumatic heart disease (RHD) is characterised by permanent damage to the valves of the heart that develops as a serious consequence of repeated episodes of acute rheumatic fever (ARF), an autoimmune reaction to a Group A streptococcus (GAS) bacterial infection. Rheumatic heart disease is a chronic cardiac condition with an infectious aetiology, causing high disease burden in low-income settings. Affected individuals are young and

associated morbidity is high. However, RHD is relatively neglected due to the populations involved and its lower incidence relative to other heart diseases.

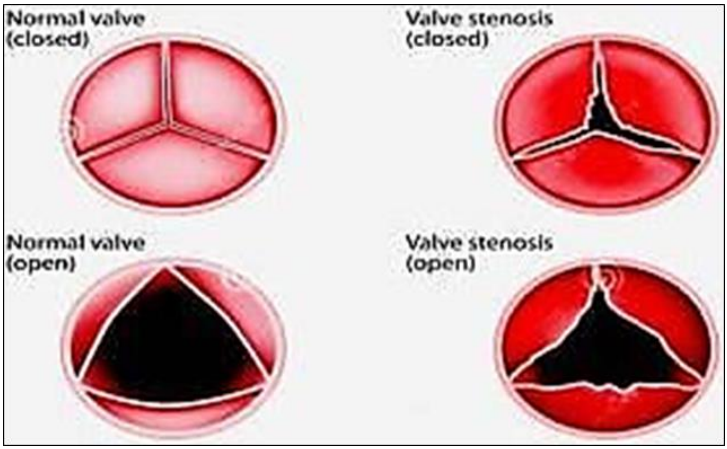


Fig 4: Rheumatic Heart disease

The resulting immune response targets both the bacteria and some of the body's own tissues that contain similar molecules to those in the bacteria, including the heart, skin, joints and nervous system.

Rheumatic heart disease results from persisting inflammation of the heart after acute or recurrent episodes of rheumatic fever. It typically affects the valves of the heart, especially the mitral and aortic valves. Chronic inflammation may cause narrowing of the valves resulting in decreased blood flow through the heart or leakage of the valves causing blood to flow in the wrong direction. This may eventually lead to arrhythmias, such as atrial fibrillation, or heart failure, where the heart is unable to pump enough blood to meet the body's needs. Rheumatic fever typically affects children between five and 15 years old for the first time but the effects of rheumatic heart disease often first present in adulthood. Environmental factors such as poor sanitation and crowded living conditions increase the transmission of the bacteria that cause rheumatic heartdisease.

Clinical Features

Rheumatic fever is a systemic illness typically presenting with fever, anorexia, lethargy and joint pains. Arthritis includes skin rashes (erythema marginatum), carditis (breathlessness, palpitations, chest pain), chorea, subcutaneous nodules and neurological features. Pulses are supporting evidence of preceding streptococcal infection: recent scarlet fever, raised

antistreptolysin O or other streptococcal antibody titers, positive throat culture.

Investigations

Blood tests may be performed in order to detect components of the inflammatory and immune responses that cause rheumatic heart disease. Diagnosis of damage to the heart is primarily achieved by echocardiography, which is an ultrasound imaging of the heart. This can detect abnormally narrow, thickened or leaky valves as well abnormal function of the heart's chambers. Rheumatic fever patients have raised ESR or c reactive protein, leukocytosis, first degree or second degree AV block.

Management

Prevention of rheumatic heart disease centers on early detection and treatment of streptococcal throat infections that cause rheumatic fever. This involves appropriate antibiotic therapy. If moderate or severe heart disease is established, an operation may be necessary to repair or replace the damaged heart valves. This may involve the insertion of a tube and balloon into the heart to dilate a narrowed heart valve through 'balloon valvotomy'. Alternatively, surgical repair or replacement of a damaged heart valve may be performed. The selection of the appropriate procedure is dependent on a number of factors, including the extent of disease of the patient and the level of expertise of the treating doctor. These procedures aim to improve symptoms and quality of life, restore heart function and prevent deterioration of the heart that may lead to complications such as arrhythmias and heart failure.

Buerger's Disease

It is characterized by acute inflammation with thrombosis involving both arteries and absent of pulses in lower limbs.

Causes: causes are unknown. May be causes are smoking, diabetes mellitus, senile atherosclerosis.

Clinical Features

Clinical features of buerger's diseases are pain in lower limbs, worse at night, better by hanging leg down. Signs are poor peripheral arterial pulsation of affected limb, low temperature in affected limb, skin is scaling, dry, colour changes are there.

Complication

Gangrene and ulceration of toes.

Diagnosis

Calcified vascular lesion in radiograph of limb, degree of obstruction in colorDoppler.

Management

Avoid exposure to cold, reduce smoking, prevent, control infection in toes, reflex heating oflimb.

Valve Heart Disease

Valvular heart disease (VHD) encompasses a number of common cardiovascular conditions that account for 10% to 20% of all cardiac surgical procedures in the United States. A better understanding of the natural history coupled with the major advances in diagnostic imaging, interventional cardiology, and surgical approaches have resulted in accurate diagnosis and appropriate selection of patients for therapeutic interventions. A thorough understanding of the various valvular disorders is important to aid in the management of patients with VHD. Appropriate work-up for patients with VHD includes a thorough history for evaluation of causes and symptoms, accurate assessment of the severity of the valvular abnormality by examination, appropriate diagnostic testing, and accurate quantification of the severity of valve dysfunction and therapeutic interventions, if necessary. It is also important to understand the role of the therapeutic interventions vs the natural history of the disease in the assessment of outcomes. Prophylaxis for infective endocarditis is no longer recommended unless the patient has a history of endocarditis or a prostheticvalve.

AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CT = computed tomography; ECG = electrocardiography; LV = left ventricular; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; RV = right ventricular.

Etiology and Pathophysiology

Isolated AR is significantly less common than pure AS. Degenerative and bicuspid aortic valve disease shows a different degree of both regurgitation and left ventricular obstruction; however, stenosis is usually pre-eminent. More frequently, AR is a consequence of aortic dilation and the deformation of the annulus valve. Overall prevalence of significant native AR has been reported in between 2.0% and 2.5% of patients 70 years to 83 years of age, without genderdifferences.

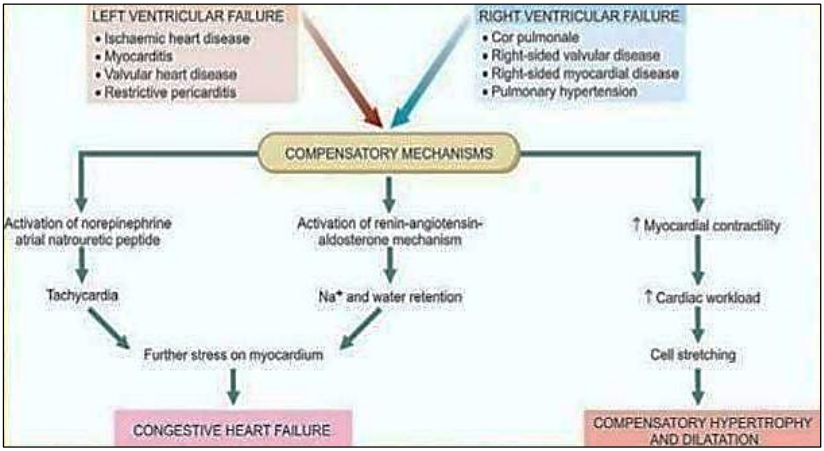


Fig 5: Valves diseases

Although smaller studies reported a higher incidence of up to 13%. Age, aortic valve fibrocalcification, and female sex were considered independent factors related to AR, while several studies failed to find a relationship with arterial hypertension.

Aortic Regurgitation

The incidence of clinically significant aortic regurgitation (AR) increases with age, typically peaking in the fourth to sixth decade of life. It is more common in men than women. The prevalence of AR in the Framingham study was reported to be 4.9%, with regurgitation of moderate or greater severity occurring in 0.5%. AR may be caused by malfunction of the valve leaflets themselves, by dilatation of the aortic root and annulus, or may be due to acombination.

Rheumatic disease is still the most common aetiology of AR in developing countries; however, in Western Europe and North America the leading cause of AR is either congenital (particularly due to bicuspid leaflets) or degenerative disease, including annuloaortic ectasia. Understanding the mechanism leading to AR is essential for proper patient management, including the surgical approach. Thus, knowledge of the morphology of the valve leaflets, the annulus and the ascending aorta are essential.

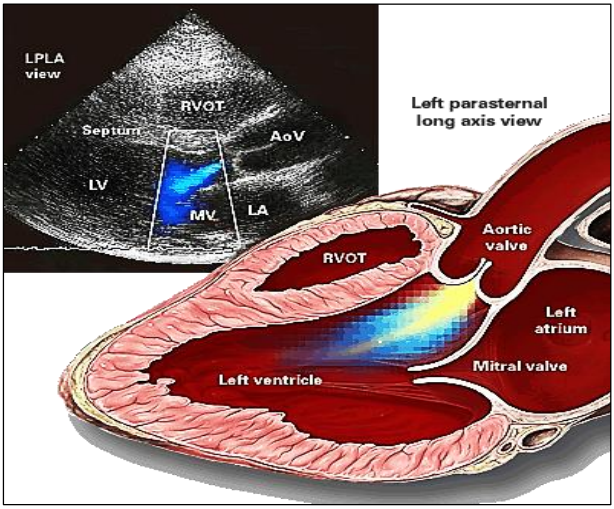


Fig 6: Aortic Regurgitation

Clinical Features

Aortic regurgitation clinical features are mild to moderate of aortic regurgitation, awareness of heart beat, palpitations, sever aortic regurgitation, heart failure, angina. Signs are large volume or 'collapsing pulse', bounding peripheral pulses, capillary pulsation in nail beds-quincke's sign, femoral bruit (pistol shot)-duroziez's sign, head nodding with pulse-de musset's sign, early diastolic murmur, systolic murmur of increased stroke volume, Austin flint murmur (soft mid diastolic), thrusting apex, fourth heart sound, enlarge LV, heartfailure.

Diagnosis

The ECG may be normal in mild AR. With greater degrees of regurgitationLVhypertrophywithorwithoutstrainpatterncanbeseen.

Chest *x* ray shows evidence of LV enlargement. Dilatation of the ascending aorta and aortic knob may be seen. Aneurysmal dilatation of the aorta can be present, particularly in patients in whom the AR is related to primary disease of the aortic wall. Echocardiography presently is the principal tool for diagnosis and grading of AR severity as well as for serial follow up. Colour Doppler is a highly sensitive and specific technique for detecting AR and provides visualisation of the regurgitant jet. Continuous and pulsed wave Doppler offer additional haemodynamic information and aid quantitation. Importantly, two dimensional echocardiography permits evaluation of LV size and function as well as visualisation of valve

structures and of the aorta. Three dimensional echocardiography may play an increasing role in obtaining more precise measurements of ventricular volumes and may offer enhanced images of valve morphology. Aortic root angiography and cardiac magnetic resonance imaging (MRI) are alternative imaging techniques, particularly in rare instances when echocardiography is technically impossible or technically limited. Radionuclide ventriculography can be used to serially assess LV ejection fraction at rest and during exercise.

Management

Treatment may be required for underlying conditions such as endocarditis or syphilis. Aortic valve replacement is indicated if aortic regurgitation causes symptoms.

Aortic Stenosis

Although valvular heart disease (VHD) is less frequent than coronary artery disease (CAD), heart failure or hypertension, it is of interest for several reasons. Aortic stenosis (AS) is a common valvular heart disease in the Western populations, with an estimated overall prevalence of 3% in adults over 75 years. To understand its patho-biological processes represents a priority. In elderly patients, AS usually involves trileaflet valves and is referred to as degenerative calcific processes. Rheumatic fever as a cause of AS already had begun to wane in developed countries and was replaced pathogenetically by degenerative calcificdisease.

The ambiguous term “degenerative” suggested that AS stemmed from wear and tear on the valve over time, perhaps explaining its greater incidence in older patients. Although calcification of the aortic valve is a disease of the elderly population, there is evidence that it is not simply a consequence of aging.

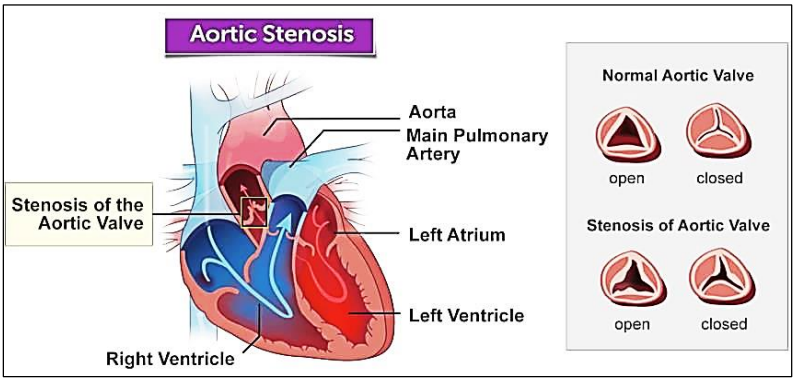


Fig 7: Aortic stenosis

Causes: In infants, children, adolescents are congenital aortic stenosis, congenital subvalvular aortic stenosis, congenital supravalvular aortic stenosis. In young adults to middle aged are calcification and fibrosis of congenitally bicuspid aortic valve, rheumatic aortic stenosis. In middle aged to elderly causes are calcification of bicuspid valve, senile degenerative aortic stenosis, rheumatic aortic stenosis.

Clinical Features

Aortic stenosis is exertional dyspnoea, pulmonary oedema, angina, exertional syncope, sudden death. Signs of aortic stenosis are ejection systolic murmur, slow rising carotid pulse, reduced pulse pressure, LVH, thrusting left ventricle, signs of left ventricular failure (Crepitations, pulmonary oedema).

Diagnosis

Electrocardiogram (ECG)-triggered CT scan of the heart and the whole aorta, including femoral and subclavian arteries, is performed. Not only can aortic annulus size be studied using MSCT but also leaflet and annulus calcification. The latter can be removed during surgery but, if present, might stand in the way of TAVI. Other important characteristics to be taken into account are distances between the annulus and the coronary ostia that could differ from standard and could result in ostial occlusion after implantation. On the other hand, left ventricular outflow tract (LVOT) and proportions of the ascending aorta are mandatory to achieve a precise and safe implantation. Moreover, the peripheral access site and the descending aorta can be evaluated for anomalies such as major calcification, stenosis, and other factors that could hinder the procedure. MSCT is now an essential tool in terms of access site evaluation, prosthesis sizing, and reducing the paravalvular leakage and risk of complications.

Management

Patients with symptomatic aortic stenosis and a valve gradient indicative of moderate or severe stenosis should have aortic valvereplacement.

Mitral Stenosis

Mitral stenosis (MS) is a form of valvular heart disease. Mitral stenosis is characterized by narrowing of the mitral valve orifice. Today, the most common cause of mitral stenosis is rheumatic fever, but the stenosis usually appears clinically relevant only after several decades.

Causes

The most common cause of mitral stenosis is rheumatic fever. Uncommon causes of mitral stenosis are calcification of the mitral valve leaflets and congenital heart disease.

Other causes of mitral stenosis include infective endocarditis, mitral annular calcification, endocardial fibroelastosis, malignant carcinoid syndrome, systemic lupus erythematosus, Whipple disease, Fabry disease, and rheumatoid arthritis. His prevalence of rheumatic disease in developed countries is declining with an estimated incidence of 1 in 100,000. The prevalence is higher in developing nations than in the United States. In Africa, for example, the prevalence is 35 cases per 100,000. Rheumatic mitral stenosis is more common in females. The onset is usually between the third and fourth decade of life.

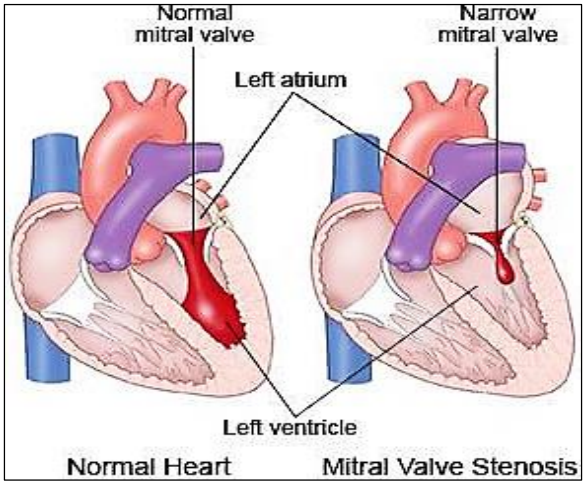


Fig 8: Mitral stenosis

Clinical Features

Mitral stenosis is exertional dyspnoea, nocturnal dyspnoea, cough, ankle/leg oedema, abdominal swelling (right heart failure), acute pulmonary oedema symptoms, secondary to arterial/venous emboli symptoms (stoke, haemoptysis, chest pain).

Signs of mitral stenosis are atrial fibrillation, mitral facies, loud 1st heart sound, opening snap mid diastolic murmur, raised pulmonary capillary pressure crepitations, pulmonary oedema, effusions, pulmonary hypertension signs, RV heave, loud P2.

Diagnosis

Mitral stenosis is evaluated using noninvasive and invasive measures. Noninvasive tests are the electrocardiogram (ECG), chest x-ray, echocardiogram, and exercise echocardiogram. An invasive test for mitral stenosis would include a cardiac catheterization. On the ECG, the P wave changes suggest left atrial enlargement. A presence of right axis deviation and right ventricular hypertrophy suggest severe pulmonary hypertension. ECG frequently detects atrial arrhythmias such as atrial fibrillation. On the chest x-ray, the early stages of mitral stenosis findings are normal heart size, straightening of the left border of the cardiac silhouette, prominent main pulmonary arteries, dilatation of the upper pulmonary veins, and displacement of the esophagus by an enlarged left atrium. During the severe chronic stage of mitral stenosis, the chest x-ray will have enlargement of all the chambers, pulmonary arteries, and pulmonary veins.

Management

Mitral stenosis is by mitral valvotomy, balloon valvuloplasty or mitral valve replacement.

Tricuspid Stenosis

Tricuspid valve stenosis (TS) is rare, affecting less than 1% of patients in developed nations and approximately 3% of patients worldwide. Detection requires careful evaluation, as it is almost always associated with left- sided valve lesions that may obscure its significance.

Primary TS is most frequently caused by rheumatic valvulitis. Tricuspid valve stenosis is usually progressive when due to rheumatic disease or carcinoid, versus a fixed stenosis in the setting of congenital abnormalities.

Moreover, most stenotic tricuspid valves have some element of tricuspid regurgitation. This is in contrast to purely regurgitant tricuspid valves, which have no element of TS. Stenotic tricuspid valves always demonstrate structural abnormalities, such as fibrous thickening of the leaflets or subvalvular mural plaque as seen in carcinoid. Each etiology of TS has its own distinct pattern of leaflet and chordal pathology.

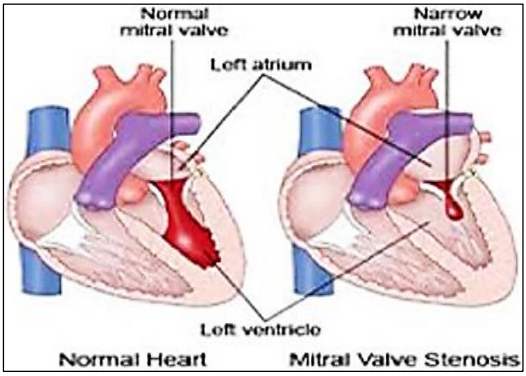


Fig 9: Tricuspid stenosis

Tricuspid stenosis is an uncommon valvular abnormality commonly associated with other valvular lesions. Ebstein's anomaly is a rare congenital heart malformation characterized primarily by abnormalities of the tricuspid valve and right ventricle. Endomyocardial fibrosis is a restrictive cardiomyopathy observed in tropical and subtropical regions. It may cause right ventricular distortion with apparent apical displacement of the tricuspid valve, mimicking Ebstein's anomaly. Eosinophilia, rheumatic in origin are the most commonly cited aetiological link in endomyocardial fibrosis.

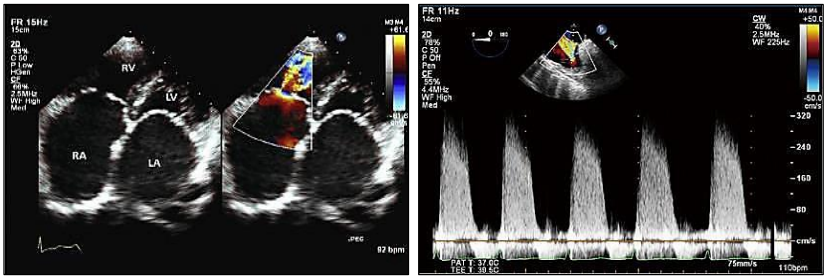


Fig 10: Tricuspid stenosis echocardiogram

Clinical Features

Tricuspid valve clinical features are mitral or aortic disease symptoms, abdominal swelling, hepatic discomfort, peripheral oedema, fatigue. Signs are raised JVP, mid diastolic murmur is increased by inspiration, right heart failure-ascites, peripheral oedema.

Management

Tricuspid stenosis is requires surgery. Either replaced or subjected to valvotomy at the time of surgery. Balloon valvuloplasty can be used to treat rare cases of isolated tricuspid stenosis.

Tricuspid Regurgitation

Tricuspid valve regurgitation (TR) presents challenges to modern day clinical practice. Its natural history is not well understood. Previously, uncertainty existed as to whether TR is an independent factor of outcome or rather a surrogate marker of right ventricular disease and other co- morbid conditions including pulmonary hypertension. However, more recently studies has shown increasing TR severity is associated with worse survival regardless of left ventricular (LV) function and pulmonary hypertension.

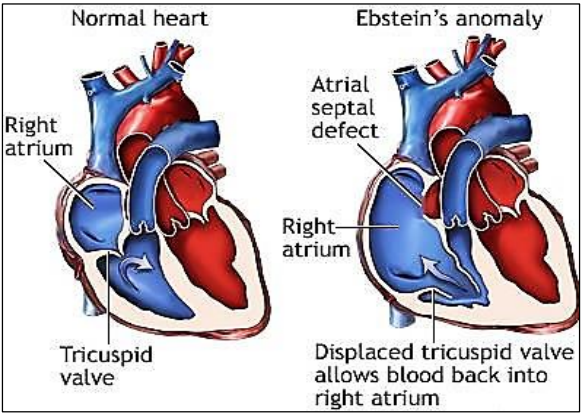


Fig 11: Tricuspid regurgitation

Primary valvular disease accounts for 10% of cases of TR in adults. Patients with congenital disease may have primary TV disease such as in Ebstein's anomaly, atrioventricular defects and myxomatous prolapse. Acquired primary conditions include endocarditis, rheumatic disease, carcinoid or flail leaflet caused by trauma. There is an increasing population of patients with isolated primary TR caused by endomyocardial biopsy or intracardiac leads. Secondary TR results from annular dilation and leaflet tethering leading tomalcoaptation.

Clinical Features

TR are rheumatic heart disease, endocarditis, particularly in intravenous drug abusers, ebstein's congenital anomaly(primary) and RV dilation due to chronic LHF, right ventricular infarction, pulmonary hypertension (secondary). Signs of tricuspid regurgitation are raised JVP, large systolic wave in JVP, pansystolic murmur (left sterna edge), systolic hepatic pulsation.

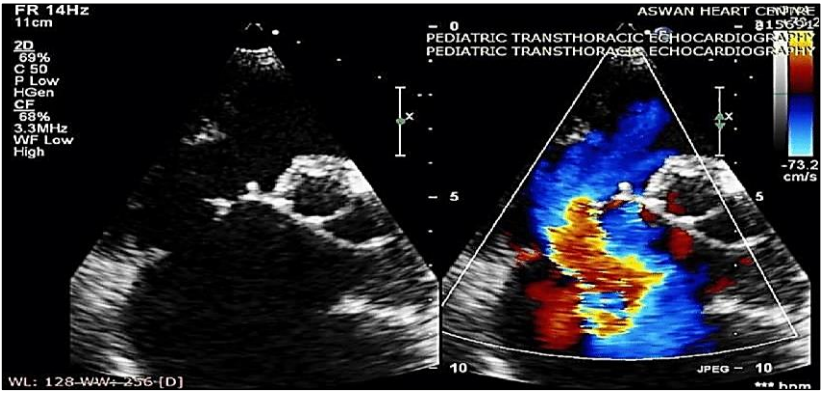


Fig 12: Tricuspid regurgitation echocardiography

Management

Tricuspid regurgitation, which is due to RV dilation, gets better when the cause of right ventricular over load is corrected.

Pulmonary Stenosis

Pulmonary stenosis is a condition characterized by obstruction to blood flow from the right ventricle to the pulmonary artery.

This obstruction is caused by narrowing (stenosis) at one or more points from the right ventricle to the pulmonary artery. Areas of potential narrowing include thickened muscle below the pulmonary valve, stenosis of the valve itself, or stenosis of the pulmonary artery above the valve. The most common form of pulmonary stenosis is obstruction at the valve itself, referred to as pulmonary valvarstenosis.

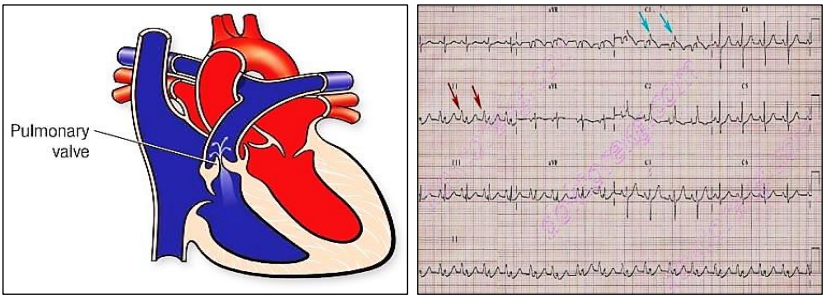


Fig 13: Pulmonary stenosis & ECG changes

Causes

Pulmonary stenosis occurs when the pulmonary valve doesn’t grow as it should or the area below or above the valve doesn't grow fully in a baby

during the first 8 weeks of pregnancy. Why this happens isn't known. Some congenital heart defects are passed down through families (genetic defects).

Clinical Features

Symptoms are right heart failure, carcinoid syndrome and signs are giant a wave in the JVP, RV hypertrophy as well as dilation, systolic murmur, systolic thrill over pulmonary outflow, P2 soft and delayed, valvular PS may have an ejection click.

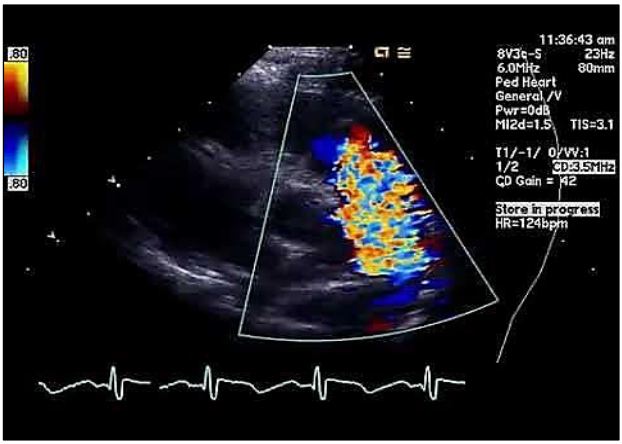


Fig 14: Pulmonary stenosis echocardiogram

Diagnosis

Echocardiogram is typically normal in the presence of mild pulmonary stenosis. With moderate-to-severe pulmonary stenosis the electrocardiogram may show enlargement of the right ventricle and thickening of its muscle. An echo uses sound waves (ultrasound) to make a moving picture of the heart and heart valves. This test is most helpful in diagnosing pulmonarystenosis.

Chest X-Ray: A chest X-ray may show changes of the heart or pulmonary artery.

ECG: An ECG records the electrical activity of the heart. It shows abnormal rhythms (arrhythmias), and finds heart muscle stress. Although the ECG is often normal, it may show abnormalities that are found with pulmonary stenosis.

Management

Mild pulmonary stenosis often does not need treatment. Moderate or severe stenosis needs repair.

Valvotomy: This is surgery to remove scar tissue from the pulmonary valve leaflets. This lets the valve open as it should.

Balloon Dilation or Valvuloplasty: A cardiac cath is done as in a diagnostic test. The catheter has a balloon on the tip. When the catheter reaches the narrowed valve or area, the provider inflates the balloon for a short time to stretch it open. Children who have had balloon dilation may need to take antibiotics to prevent heart infection after being discharged from thehospital.

Valvotomy: This is surgery to remove scar tissue from the pulmonary valve leaflets. This lets the valve open as it should.

Pulmonary Regurgitation

Isolated pulmonary regurgitation, in an otherwise normal heart, is well tolerated for decades. However, in a meta-analysis reported in the literature, 29% of patients had developed symptoms within 40 years. Many patients with a right ventricle to pulmonary artery conduit develop a mixture of obstruction and regurgitation across the conduit. However, some of these patients have regurgitation as the dominant lesion, and feature in pulmonary valve replacement series. In pulmonary regurgitation secondary to pulmonary hypertension, the clinical picture is dominated by the primary lung disease or the high pulmonary vascular resistance rather than the volume load. Severe acute pulmonary regurgitation driven by a large duct can occur in neonatal Ebstein's anomaly or following balloon dilation of critical pulmonary stenosis or perforation of valvar pulmonary atresia.

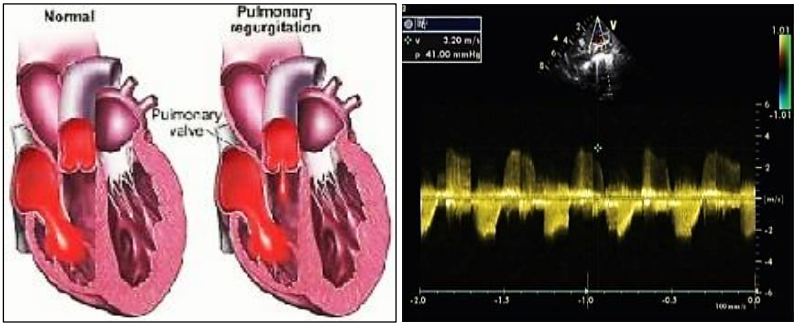


Fig 15: Pulmonary regurgitation & echocardiogram

Causes

Infection endocarditis, complication after surgery to repair tetralogy of fallot, carcinoid syndrome, rheumatic fever and complications after catheterization are rare causes in the India.

Clinical Features: murmurs, chest pain, discomfort, fatigue, lightheadedness or fainting.

Management

Pulmonary regurgitation is usually focused on the underlying cause that created the valve problem (e.g. pulmonary hypertension). The need to replace the pulmonary valve is very rare.

Infective Endocarditis (IE)

It is due to rare, life-threatening disease that has long lasting effects even among patients who survive and are cured. IE disproportionately affects those with underlying structural heart disease and is increasingly associated with healthcare contact, particularly in patients who have intravascular prosthetic material. In the setting of bacteraemia with a pathogenic organism, infected vegetation may form as the end result of complex interactions between invading microorganisms and the host immune system. Once established, IE can involve almost any organ system in the body. The diagnosis of IE may be difficult to establish and a strategy that combines clinical, microbiological and echocardiography results has been codified in the modified Duke criteria. In cases of blood culture-negative IE, the diagnosis may be especially challenging and novel microbiological and imaging techniques have been developed to establish its presence. Once diagnosed, IE is best managed by a multidisciplinary team with expertise in infectious diseases, cardiology and cardiac surgery. Antibiotic prophylaxis for the prevention of IE remains controversial. Efforts to develop a vaccine targeting common bacterial causes of IE are ongoing, but have not yet yielded a commercially available product.

IE is a relatively rare but life-threatening disease.In a systematic review of the global burden of IE, crude incidence ranged from 1.5 to 11.6 cases per 100,000 person-years, with high quality data availablefrom only 10-mostly high-income-countries.

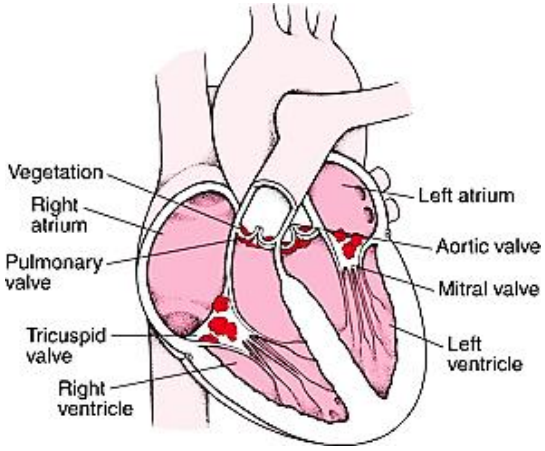


Fig 16: Endocarditis

Causes

It is cause are bacteria like streptococci (viridians 30 -40%), enterococci (10-15%), other streptococci (20-25%).

Pathophysiology

Experimentally, the normal valvular endothelium is resistant to bacterial colonization upon intravascular challenge. Thus, the development of IE requires the simultaneous occurrence of several independent factors: alteration of the cardiac valve surface to produce a suitable site for bacterial attachment and colonization; bacteraemia with an organism capable of attaching to and colonizing valve tissue; and creation of the infected mass or 'vegetation' by 'burying' of the proliferating organism within a protective matrix of serum molecules (for example, fibrin) and platelets.

Clinical Features

Clinical features of endocarditis are cerebral emboli, subconjunctival haemorrhages, varying murmurs, conduction disorders, cardiac failure, haematuria, osler's nodes, systemic emboli, petechial rash, loss of pulses, roth's SPOS in fundi, petechial haemorrhages on mucous membranes and fundi, splenomegaly, digital clubbing, splinter haemorrhages, weight loss, night sweats, fever, tiredness, develops new signs of valve dysfunction or heart failure.

Investigations

The diagnosis of IE typically requires a combination of clinical, microbiological and echocardiography results. Historically, and as is

probably still the case in resource-limited settings, IE was diagnosed clinically based on classic findings of active valvulitis (such as cardiac murmur), embolic manifestations and immunological vascular phenomena in conjunction with positive blood cultures. These manifestations were the hallmarks of subacute or chronic infections, most often in young patients with rheumatic heart disease. In the modern era in developed countries, however, IE is usually an acute disease with few of these hallmarks because the epidemiology has shifted towards healthcare-associated IE, often with early presentations due to *S. aureus.* Blood culture is the most important initial laboratory test in the workup of IE. Bacteraemia is usually continuous and the majority of patients with IE have positive blood cultures. Echocardiography is the second cornerstone of diagnostic efforts and should be performed in all patients in whom IE is suspected. Transthoracic echocardiography (TTE) may enable visualization of vegetations in many patients. These include 3D TEE, cardiac CT, cardiac MRI and F-fluorodeoxyglucose PET-CT.

Blood Culture Positivity for Either of the following

- Typical microorganism (viridans group streptococci, *S. gallolyticus*, HACEK organisms, *S. aureus*, community acquired enterococci in the absence of a primary focus) from 2 separate bloodcultures.
- Persistent bacteremia (two positive cultures >12 hours apart or three positive cultures or a majority of ≥4 culture positive results >1 hour apart).

Serology

Single positive blood culture for C. Burnetii or antiphase 1 IgG antibody titre of more than 1:800.

Thus, IE diagnosis cannot be made on the basis of a single symptom, sign or diagnostic test. Rather, the diagnosis requires clinical suspicion, most commonly triggered by systemic illness in a patient with risk factors.

Followed by evaluation according to the diagnostic schema outlined in the modified Duke criteria. It is worth keeping in mind that the Duke criteria were originally developed to facilitate epidemiological and clinical research efforts and the application of the criteriatotheclinicalpractice setting is more difficult.

Management

In the modern era, management of IE typically requires a multidisciplinary team including, at a minimum, an infectious disease

specialist, a cardiologist and a cardiac surgeon. All patients should receive antimicrobial therapy and a subset may benefit from cardiovascular surgical intervention.

Cardiomyopathy

It is a genetic disorder of cardiac myocytes that is characterized by cardiac hypertrophy, unexplained by the loading conditions, a non-dilated left ventricle and a normal or increased ejection fraction. Cardiac hypertrophy is usually asymmetric with greatest involvement most commonly of the basal interventricular septum subjacent to the aortic valve.

It is occasionally restricted to other myocardial regions, such as the apex, the mid-portion as well as the posterior wall of the left ventricle. At the cellular level, cardiac myocytes are hypertrophied, disorganized, and separated by areas of interstitial fibrosis. A diverse array of mechanisms, mirroring the diversity of the causal genes and mutations, are implicated in the pathogenesis of HCM. The mechanistic events in HCM might be categorized into four sets of interlockingmechanisms.

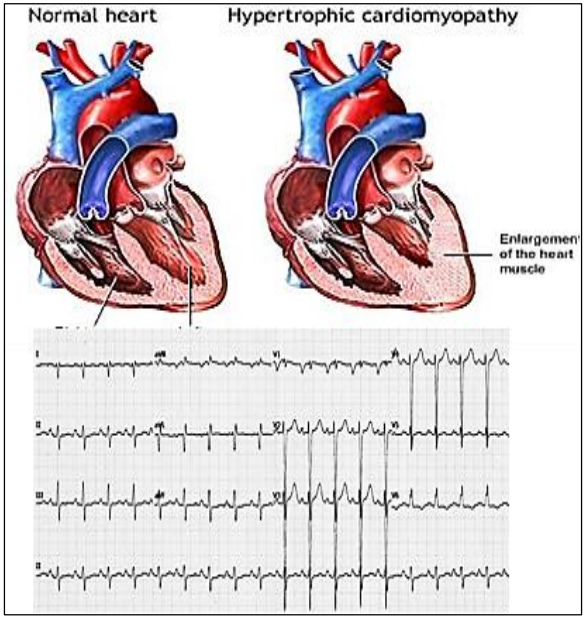


Fig 17: Cardiomyopathy & ECG

The primary defect is the mutation. Initial or proximal phenotypes are defined as those resulting from the direct effects of the mutations on the structure and function of the sarcomere proteins. The intermediary (or

secondary) phenotypes include the molecular changes that occur in response to the changes in the sarcomere protein structure and function. Examples of the latter include altered gene expression and activation of the signaling pathways, such as the MAPK and TGFB1pathways.

The tertiary effects are the ensuing histological and pathological phenotypes, which are the consequence of perturbation of a myriad of secondary molecular events in the myocardium, such as activation of the hypertrophic signaling pathways. These molecular and histological changes lead to the clinical phenotypes of HCM (quaternary). It is important to note that there is a mechanistic distinction between cases of HCM caused by sarcomere protein mutation and the phenocopy conditions, since ventricular hypertrophy in the latter may, at least in part, result from storage of material, such as glycogen and in part because of functional defects in myocytes, such as impairedcontraction.

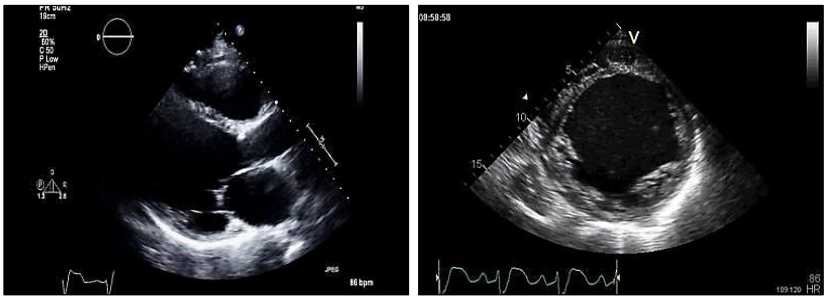


Fig 18: Cardiomyopathyechocardiogram

Clinical Features

Angina on effort, dyspnoea on effort, syncope, sudden death. Signs of Cardiomyopathy is jerky pulse, palpable left ventricular hypertrophy, double impulse at the apex, mid systolic murmur at the base, pansystolic murmur, signs of left ventricular out flow tract obstruction which may be augmented by standing up, inotropes and vasodilators.

Diagnosis

ECG in patients with idiopathic DCM has no specific diagnostic role, and abnormalities ranging from isolated T wave and ST segment changes to septal pathological Q waves, wide QRS complex in patients with LV fibrosis might be present.

Prolongation of atrioventricular (AV) conduction, and bundle branch block can be observed. Echocardiography in DCM has characteristic patterns, although it is not possible to make differential diagnosis by

echocardiography between idiopathic and other secondary LV dilation with dysfunction. M-mode echocardiography shows LV dilation with diffuse hypokinetic walls. Although cardiomyopathy is diffuse pathology, there may be segmental differences of the degree of hypokinesis revealed by two dimensional echocardiography, which causes difficulties for differentiation from ischemic cardiomyopathy. Ventricular dilation usually is not accompanied by sufficient hypertrophy, which causes increase of volume-to-massratio.

Management

Beta adrenoceptor antagonists help to relieve angina and sometimes prevent syncopal attacks but no pharmacological treatment is definitely known to improve prognosis.

Pericarditis

Pericarditis is a common disorder caused by inflammation of the pericardium and can occur as an isolated entity or as a manifestation of an underlying systemic disease. It is diagnosed in approximately 0.1% of hospitalized patients and in 5% of patients admitted to the emergency department with noncardiac chest pain. In most patients, the cause of acute pericarditis is thought to be idiopathic because the yield of diagnostic tests to confirm etiology has been relativelylow.

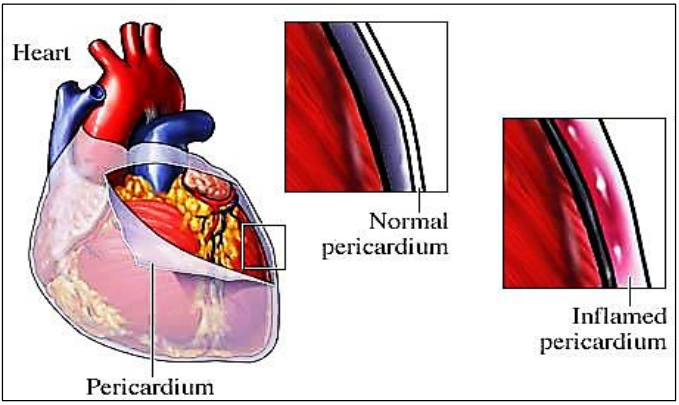


Fig 19: Pericarditis

Etiology

Acute myocardial infraction, viral, uraemia, malignant disease, trauma (blunt chest injury), connective tissue disease (SLE), bacterial infection, rheumatic fever, tuberculosis.

Clinical Features

Pericarditis symptoms are retro eternal pain and radiates to the shoulders and neck. Pain worst by deep breathing, movement, a change of position, exercise and swallowing, low grade fever.

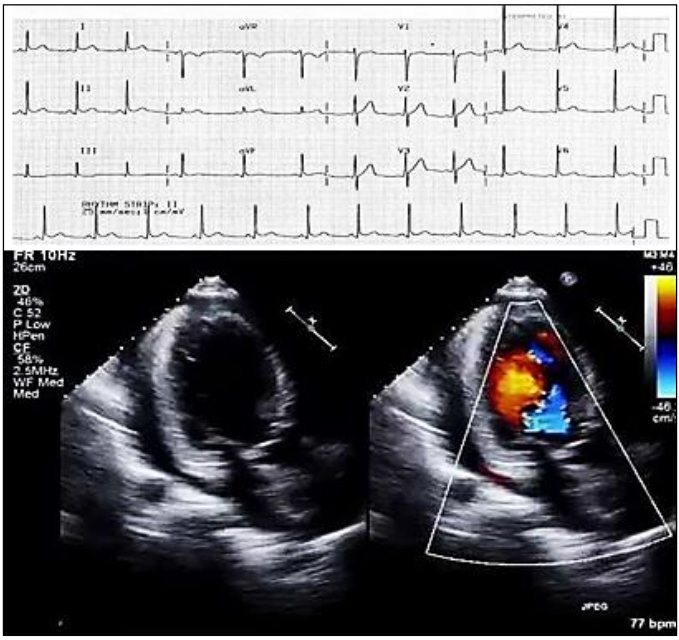


Fig 20: Pericarditis ECG & echocardiogram

Diagnosis

Typical ECG changes in acute pericarditis include wide-spread upward concave ST-segment elevation and PR-segment depression.

Transthoracic echocardiography is recommended in patients with suspected acute pericarditis who have evidence of hemodynamic compromise. The finding of a significant pericardial effusion supports the diagnosis and guides further management, especially if there is evidence of cardiac tamponade and a need for emergentpericardiocentesis.

Management

The pain can usually be relieved by NSAID's, anti-inflammatory agents may be required. Purulent pericarditis requires treatment with antimicrobial therapy, if necessary, surgical drainage.

Chapter - 2

Diseases of the Endocrinology

Thyroid Gland

The thyroid gland secrets predominantly thyroxine (T_4), and only a small amount of triiodothyronine (T_3); approximately 85% of $T_3$is produced by monodeiodination of T_4in other tissues such as liver, muscle and kidney. T_4 is probably not metabolically active until converted to T_3 and may be regarded as a prohormone. Thyrotropin releasing hormone (TRH) come from hypothalamus and converted to Thyroid stimulation hormone (TSH) at glands/targets levels, T_3, T4 at target hormones. There is a negative feedback of thyroid hormones on the thyrotrophs such that in hyperthyroidism, when plasma concentrations of T3 and T4 are raised. TSH secretion is suppressed and in hypothyroidism due to disease of the thyroid gland low T3 and T4 are associated with high circulating TSH levels. The anterior pituitary is very sensitive to minor changes in thyroid hormone levels within the normal range. Although the reference range for total T4 is 60-150 nmol/l, a rise or fall of 20 nmol/l in an individual in whom the levels is usually 100 nmol/l would on the one hand be associated with undetectable TSH and o the other hand with a raised TSH. The combination of normal T3 and T4 and suppressed or raised TSH is known as “sub clinical hyperthyroidism and sub clinical hypothyroidism respectively”. Excessive circulating levels of free thyroid hormones called ‘hyperthyroidism’ and decreased circulating levels of free thyroid hormones called ‘hypothyroidism’.

Hyperthyroidism

Hyperthyroidism is the clinical syndrome which results from exposure of the body tissues to excess circulating levels of free thyroid hormones. It is a common disorder with a prevalence of about 20/1000 females; male are affected five times less frequently. In over 90% of patients hyper thyroidism is due to Graves’ disease, multinodular goiter or an autonomously function solitary thyroid nodule (toxic adenoma). It may be caused by any one of the following:

a) Graves' disease
b) Toxic multinodular goiter

c) Toxic solitary nodule ("hot" nodule)
d) Ingestion of thyroid hormones (thyrotoxicosis factitia)
e) Subacute thyroiditis
f) Chronic thyroiditis
g) TSH-producing pituitary adenoma
h) Trophoblastic tumors (choriocarcinoma or hydatidiform mole)
i) Thyroid carcinoma
j) Struma ovarii

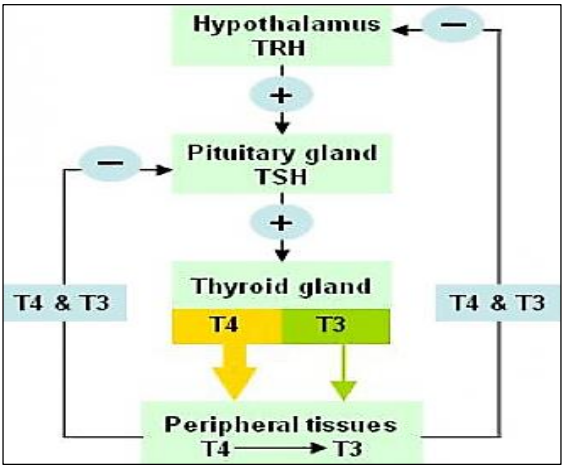


Fig 1: Background of thyroid gland

Graves's Disease

The most common cause of hyperthyroidism in iodine sufficient areas is Graves' disease. In Sweden, the annual incidence of Graves' disease is increasing, with 15-30 new cases per 100 000 inhabitants in the 2000. The cause of Graves' disease is thought to be multifactorial, arising from the loss of immunotolerance and the development of autoantibodies that stimulate thyroid follicular cells by binding to the TSH receptor. Several studies have provided some evidence for a genetic predisposition to Graves' disease. The genes involved in Graves' disease are immune- regulatory genes and thyroid autoantigens such as the thyroglobulin and TSH-receptor genes. Given the higher prevalence of Graves' disease in women, sex hormones and chromosomal factors, such as the skewed inactivation of the X chromosome, are suspected to be triggers. Other factors such as infection, vitamin D and selenium deficiency, thyroid damage, and immunomodulating drugs are also suspected.

Causes	Frequency (%)
Graves disease	76
Multinodular goiter	14
Autonomously functioning solitary thyroid nodule	5
Thyroiditis	3
Iodide induced e.g.drugs etc.,	1
Extra thyroidal source of thyroid hormone excess	0.2
TSH induced	0.2
Follicular carcinoma + metastases	0.1

Pathogenesis

Graves' disease is an autoimmune disorder caused by antibodies that bind to and stimulate the TSH receptor (TSHR), often called thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulin (TSI). These oligoclonal IgG antibodies act as TSH agonists. They are specific for the disorder and are found in 80% to 100% of untreated patients. TSH receptor antibodies can have different grades of functional activity determined by the differences in conformational molecular binding that induces structural changes in the TSH receptor. Those that bind to the ectodomain, or extracellular portion of the TSHR, with high affinity are stimulating in nature, whereas antibodies that recognize various other epitopes are less stimulatory, neutral, or even blocking. Multiple antibodies may be present in an individual patient and the degree of thyroid stimulation is determined by the bioactivity and relative concentration of the different antibodies. More recently, it has been suggested that the extracellular A-subunit of the TSH receptor is the predominant immunogen in Graves' disease. Timers of the subunit, either shed from a trimeric holoreceptor or components that have undergone multimerization to form trimers, are responsible for pathologic antibody formation. Evidence comes from studies showing that immunization with purified TSHR-A subunit produced only nonfunctioning antibodies. Mouse models of Graves' disease have been successfully established by immunization with recombinant adenovirus vectors expressing the A- subunits of the TSHR.

TSHR-stimulating antibodies activate the TSHR, resulting in binding of Gs/Gq proteins that trigger cyclic AMP (cAMP) and inositol trisphosphate (IP3)-mediated pathways.

This promotes thyroid growth, increased vascularity, iodide uptake, and increased thyroid hormone production and release. Different mechanisms have been proposed to explain the development of autoimmunity in Graves' disease and include the following:

Failure of activated T cells to undergo anergy, deletion, and apoptosis: The development of self-tolerance occurs by a process of elimination of self-reacting T cells during the process of maturation in the thymus and peripheral immune system. There is a combination of both positive and negative selection and T-cells reactive to endogenous peptides are triggered to undergo apoptosis. When self-reactive T-cells escape deletion, such as those recognizing thyroid antigens [TSH receptor, thyroid peroxidase (TPO), thyroglobulin], an autoimmune process is initiated.

Bystander Activation of Thyroidal T-Cells

This refers to activation of thyroid specific T cells in susceptible individuals indirectly as a result of inflammation [via cytokines, such as interferon (IFN)-γ] produced by non-thyroid specific bystander immune cells which could have arisen from an infection and infiltrated the thyroid gland. This phenomenon of T-cell activation has been demonstrated in animal models of thyroiditis. Expression of major histocompatibility complex (MHC) Class II molecules by the thyroid cells: Thyroid cells in general do not express MHC molecules, which are essential for the presentation of antigens to immune cells. Epithelial cells from patients with autoimmune thyroid disease over express MHC/human leucocyte antigen (HLA) class II molecule which leads to an augmentedpresentation of thyroid antigens and activation of thyroid specific T-cells. MHC molecule expression can be induced by cytokines and interferon's produced in the thyroid gland from an infection ortrauma.

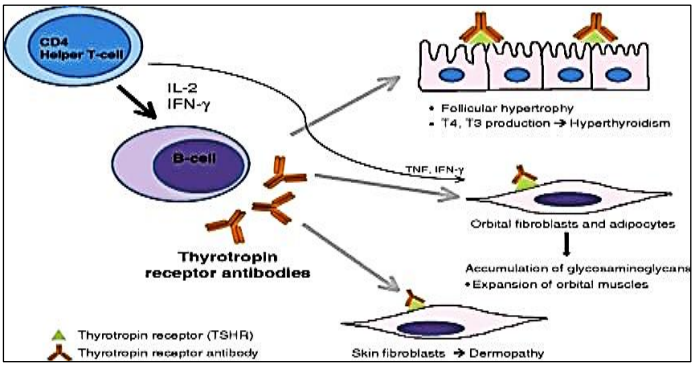


Fig 2: Pathogenesis of gravesdisease

Clinical Features

Hyperthyroidism usually develops insidiously and most patients have had symptoms for at least six months before presentation. Almost every

system is affected and the clinical feature are goiter (diffuse + bruit, nodular), weight loss despite normal or increased appetite, hyperdefecation, diarrhoea, steatorrhoea, anorexia, vomiting, sinus tachycardia, atrial fibrillation, increase pulse pressure, angina, cardiomyopathy, cardiac failure, dyspnoea, asthma, tremor, muscle weakness, proximal myopathy,periodic paralysis, increased sweating, alopecia, pigmentation, vitiligo, pretibial myxoedema, amenorrhoea, infertility, spontaneous abortion, loss of libido, impotence, diplopia, loss of visual acuity, heat intolerance, fatigue, gynaecomastia, thirst, osteoporosis.

Graves' Ophthalmopathy

The cardinal feature is accumulation of hydrophilic glycosaminoglycans in the orbital muscles and the connective tissue, which causes swelling and edema. Glycosaminoglycans are produced by the stimulation of orbital fibroblasts and adipocytes by cytokines from activated T-cells that infiltrate the orbit. TSHR and insulin-like growth factor 1 (IGF-1) receptors (IGF-1R) are expressed by orbital fibroblasts in higher quantities in individuals with thyroid-associated ophthalmopathy than in healthy individuals. *In vitro*, stimulation of orbital fibroblasts with TSH and IGF-1 cause a synergistic increase in glycosaminoglycans production. Stimulation of the receptor by TRAbs activates an inflammatory response and cytokine production; though it is still not known if the TSHR in the orbital tissues acts as the primary antigen that initiates the autoimmune response. A role of stimulatory IGF-1R autoantibodies has also been proposed but is still questionable. A recent study by Krieger *et al*. showed no evidence of IGF-1R stimulating antibodies in patients with Graves' ophthalmopathy, but demonstrated immunoglobulins that bind to TSHR and then result in a cross talk with the IGF-1R leading to its activation. The presentation of Graves' ophthalmopathy can range from being a very mild disease to potentially eyesight threatening severe disease that could be irreversible. Symptoms include eyelid retraction, edema, proptosis, a pressure-like sensation at the back of the eyes, dry eyes, foreign body or gritty sensation in the eyes, tearing, photophobia, optic neuropathy, and cornealulceration.

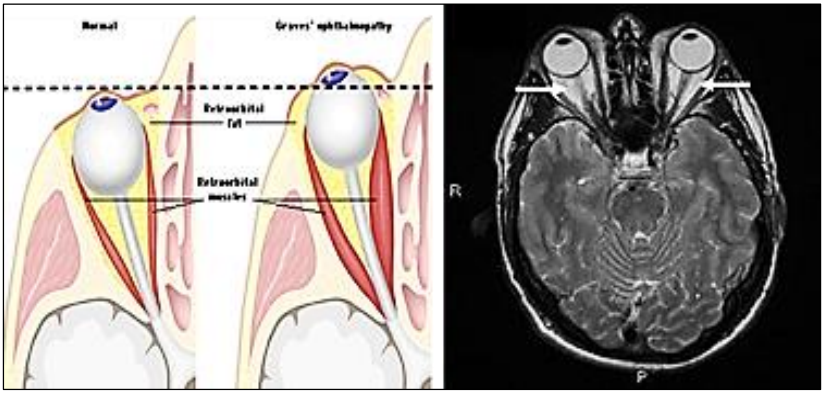


Fig 3: Different between normal graves opthalmopathy and CT image

Diagnosis

Serum TSH should be measured first, because it has the highest sensitivity and specificity in the diagnosis of thyroid disorders. If low, serum freeT_4 or free T_4 index, and free or total T_3concentrations should be measured to distinguish between subclinical hyperthyroidism. It also identifies disorders with increased thyroid hormone concentrations and normal or only slightly raised TSH concentrations, as in patients with TSH-secreting pituitary adenomas or peripheral resistance to thyroid hormone. A thyroid radioactive iodine uptake test in patients with Graves' disease would show diffusely increased uptake. However, radioactive iodine uptake would be normal or high with an asymmetrical and irregular pattern in toxic multinodular goitre, and a localised and focal pattern in toxic adenoma, with suppressed uptake in the remaining thyroid tissue. Radioactive iodine uptake in patients with thyrotoxicosis from extrathyroidal sources of thyroid hormone or from release of preformed thyroid hormones, as in silent or painful thyroiditis, will be very low. Thyroid ultrasound and thyroid radioactive iodine uptake have similar sensitivity for the diagnosis of Graves' disease (95·2% and 97·4%, respectively). Advantages of ultrasound are absence of exposure to ionising radiation, and higher accuracy in the detection of thyroid nodules and lower cost than with radioactive iodineuptake.

Management

It can be manage with anti-thyroid drugs and constitute homoeopathic medications.

Parathyroid Gland

The parathyroid glands are unique organs responsible for maintaining the critical function of calcium homeostasis. There are commonly four parathyroid glands that weigh approximately 40 grams each and are generally located posterior and inferior to the thyroid in the neck. These organs secrete parathyroid hormone (PTH), which controls calcium regulation. Secretion of PTH is modulated not only by serum calcium but also phosphorus and vitamin D through negative and positive feedback loops. In the bone, PTH binds to PTH type 1 receptors (PTH1R) to assist with calcium resorption. In the kidney, PTH acts to increase renalcalcium, decrease phosphate reabsorption, and activate metabolism of vitamin D. In the intestine, PTH transcriptionally upregulates 1 alpha hydroxylase, leading to increased production of 1,25-dihydroxyvitamin D, which in turn enhances calcium and phosphorus reabsorption. These actions of PTH on the bones, kidneys, and intestines are a careful orchestration of interrelated processes driven by feedback loops. Subsequently, excessive or insufficient secretion of PTH can lead to disruption of these loops and, in turn, alterations in calcium homeostasis. Both the direct action of PTH on the heart and alterations of calcium homeostasis (e.g., hypercalcemia or hypocalcemia) comprise the two primary mechanisms by which diseases of the parathyroid affect the cardiovascular system. In recent years, clinical and molecular research has bolstered awareness of several cardiovascular complications that are associated with parathyroid disorders-namely, hypertension, arrhythmias, heart failure, and calcific disease of vessels andvalves.

Primary Hyperparathyroidism

One of the more common disorders of the parathyroid glands is primary hyperparathyroidism (PHPT), an overproduction of PTH thatsubsequently leads to hypercalcemia. This is most commonly due to a solitary parathyroid adenoma, but about 15% of cases can be caused by diffuse hyperplasia of the glands.5While the typical complications and symptoms of PHPT are well known (e.g., nephrolithiasis, osteoporosis, constipation, and weakness), cardiovascular complications are increasingly gainingrecognition.

Indeed, patients with symptomatic PHPT have increased mortality due to myocardial infarction, stroke, and other cardiovascular causes, and they also have increased all-cause mortality.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism (SHPT) is seen early in chronic kidney disease (CKD) and is almost always present in ESRD. While the exact

sequence of events leading to SHPT is not definitively established, it is generally thought to be driven early on by disturbances in renal phosphate handling and by the more recently discovered bone-derived fibroblast growth factor 23. In fact, even small decreases in calcium levels caused by these processes are enough to stimulate the parathyroid to secrete PTH. Secondary hyperparathyroidism is an important contributor to cardiovascular mortality in ESRD and CKD, especially in more advanced stages. Indeed, in ESRD patients, the 5-year mortality is as high as 50%, with CVD as the leading cause of death, and is not explained solely by traditional risk factors such as age, diabetes, and smoking.

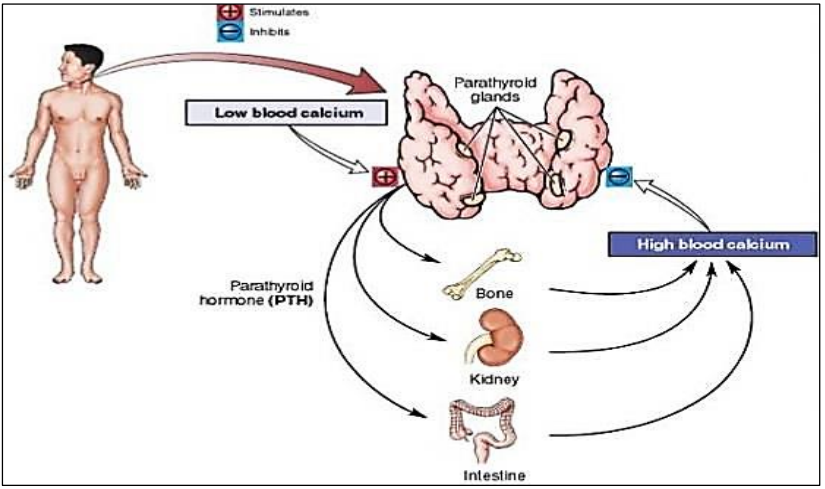


Fig 4: Parathyroid gland

Excess PTH (as seen in primary and secondary hyperparathyroidism) is associated with a higher incidence of hypertension, left ventricular hypertrophy, heart failure, cardiac arrhythmias, and valvular calcific disease, which may contribute to higher cardiac morbidity andmortality.

Hypoparathyroidism

Hypoparathyroidism is an uncommon condition characterized by absent or low PTH levels, hypocalcemia, and hyperphosphatemia. The etiology of hypoparathyroidism is broad and can be congenital or acquired.

For example, DiGeorge syndrome, which is due to a chromosomal deletion at 22q11.2, is characterized by parathyroid hypoplasia in addition to cardiac defects, thymic hypoplasia, neurocognitive problems, and renal and skeletal abnormalities, among others. The cardiac effects from hypoparathyroidism stem from the resulting hypocalcemia.

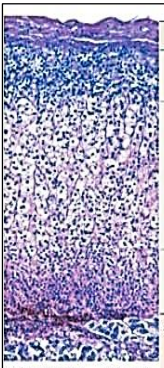
For example, hypocalcemia causes QT prolongation, which can predispose patients to potentially life threatening arrhythmias. Additionally, dilated cardiomyopathy from chronic hypocalcemia is a well-known but uncommon complication. Decreased PTH states (as seen in congenital and acquired disorders of the parathyroid glands) are associated with cardiac arrhythmias and dilated cardiomyopathy.

Management

The most common treatment is to remove the enlarged gland (or glands). This surgery cures the problem 95 percent of the time. Instead of surgery, some people with mild or no symptoms of primary hyperparathyroidism may decide to try hormone replacement therapy or medicationoptions.

Adrenal Gland

Adrenal gland is divided in to 3 zones. Those are zona glomerulosa, zonae fasciculate and reticulans in cortex region. Zona glomerulosa will release aldosterone (angiotensin II), zonae fasciculate release cortisol (ACTH) and zona reticulans release adrenal androgens (ACTH principal stimuli). Do to sympathetic nervous system will release adrenaline, nor adrenaline in medulla region.



Region/Zone	Hormones	Primary Target	Hormonal Effects	Regulatory Control
ADRENAL CAPSULE				
ADRENAL CORTEX Zona glomerulosa	Mineralocorticoids, primarily aldosterone	Kidneys	Increase renal reabsorption of Na^+ and water (especially in the presence of ADH), and accelerate urinary loss of K^+	Stimulated by angiotensin II, elevated blood K^+ or fall in blood Na^+; inhibited by ANP and BNP
Zona fasciculata	Glucocorticoids (cortisol [hydrocortisone], corticosterone)	Most cells	Increase rates of glucose and glycogen formation by the liver; release of amino acids from skeletal muscles, and lipids from adipose tissues; promote peripheral utilization of lipids; anti-inflammatory effects	Stimulated by ACTH from the anterior lobe of the pituitary gland
Zona reticularis	Androgens	Most cells	Adrenal androgens stimulate the development of pubic hair in boys and girls before puberty.	Androgen secretion is stimulated by ACTH.
ADRENAL MEDULLA	Epinephrine (E), norepinephrine (NE)	Most cells	Increases cardiac activity, blood pressure, glycogen breakdown, blood glucose levels; releases lipids by adipose tissue	Stimulated by sympathetic preganglionic fibers

Fig 5: Adrenal Hormones

Principal function of adrenal hormones glucocorticoids: carbohydrate metabolism regulation, increase protein catabolism, immunomodulation, cardiovascular regulation. In mineralocorticoids are sodium retention, potassium excretion. In catecholamines are increase heart rate, modulate vascular tone (vasoconstriction by noradrenaline and vasodilation by adrenaline), antagonize insulin action.

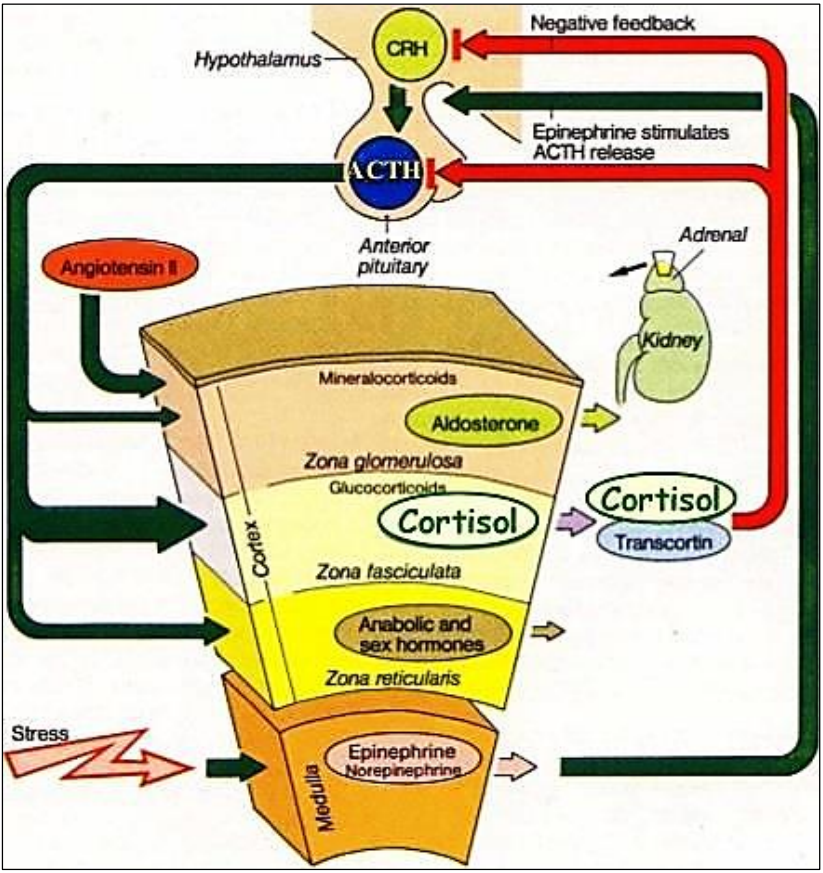


Fig 6: Regulation of adrenal gland secretion

Hyperfunction of the Adrenal Gland

Excess glucocorticoid caused formed Cushing's syndrome.

Cushing's syndrome

Cause of cushing syndrome are classified as a ACTH dependent: Pituitary dependent bilateral adrenal hyperplasia (i.e. cushing disease), ectopic ACTH syndrome (bronchial carcinoid, small cell lung carcinoma, pancreatic carcinoma), iatrogenic (ACTH therapy) (or) Cushing's syndrome, a potentially lethal disorder characterized by endogenous hypercortisolism, may be difficult to recognize, especially when it is mild and the presenting features are common in the general population. However, there is a need to identify the condition at an early stage, as it tends to progress, accruing additional morbidity and increasing mortality rates. Once a clinical suspicion

is raised, screening tests involve timed measurement of urine, serum or salivary cortisol at baseline or after administration of dexamethasone, 1 mg. Each test has caveats, so that the choice of tests must be individualized for each patient. Once the diagnosis is established, and the cause is determined, surgical resection of abnormal tumor/tissue is the optimaltreatment.

When this cannot be achieved, medical treatment (or bilateral adrenalectomy) must be used to normalize cortisol production.

Non ACTH depend are iatrogenic (chronic glucocorticoid therapy e.g. for asthma), adrenal adenoma, adrenal carcinoma. Pseudo Cushing syndrome, i.e. cortisol excess as part of another illness are alcohol excess, major depressive illness, primary obesity (mild biochemical features, some clinicaloverlap).

Clinical Features

Weight loss, menstrual irregularity, hirsutism, psychiatric, backache, muscle weakness, central obesity, plethora, moon face, hypertension, bruising, striae, muscle weakness presented.

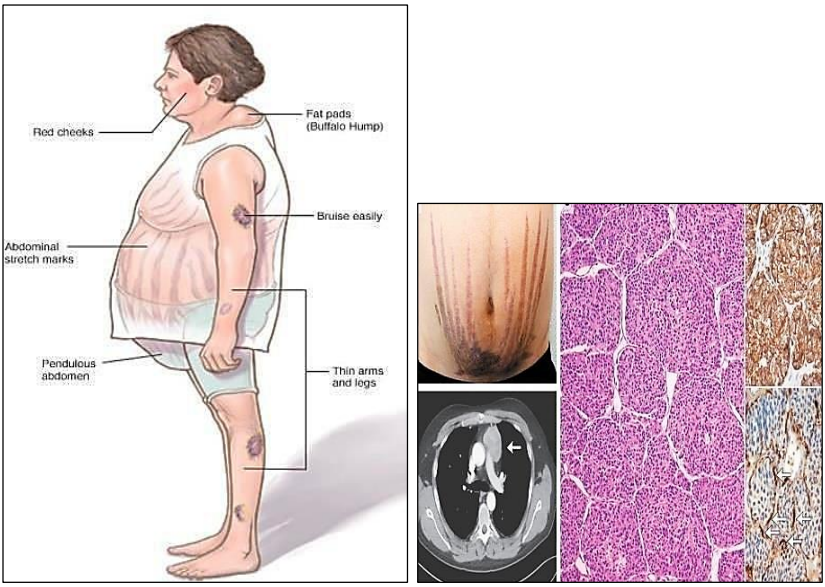


Fig 7: Cushing syndrome

Investigations

A clinical practice guideline from the Endocrine Society recommends use of at least two of three different screening tests: 24-hour urine free

cortisol (UFC) excretion, late night/bedtime salivary cortisol levels and the 1 mg overnight dexamethasone suppression test (DST; or alternatively the 2 mg 2-day DST). The screening tests all reflect different physiologic abnormalities in Cushing's syndrome: high integrated daily cortisol production (UFC), loss of bedtime salivary or serum cortisol nadir, and impaired response to glucocorticoid negative feedback. Thus, they are complimentary, and the use of more than one test is extremely helpful, as the results generally should corroborate eachother.

Other tests have not been widely validated for this use (e.g., 0.5 mg DST, fractional overnight UFC), or are not widely available (24-hour 17-hydroxycorticosteroid excretion), and are not recommended. The result of each cortisol screening test (saliva, serum, urine) is considered normal if it falls within the normal reference range; cortisol values 8 hours after administration of 1 mg dexamethasone at 2,300 to 2,400 hours should normally be <1.8 µg/dL (50 nmol/L). Because of this, prescribers of a screening test must know about certain characteristics of the cortisol assay used to measure the result, to avoid misinterpretation.

Management

This is essential, as untreated Cushing's syndrome has a 50% – 60% five year mortality. Most patients are prepared for surgery with medical therapy for a few weeks.

Hypofunction of the Adrenal Gland

Addison's disease

This is a rare condition with an estimated incidence in the developed world of eight cases per million populations. However, adrenal insufficiency is a well-recognized complication in patients with AIDS and may result from a variety of causes including tuberculosis, fungal and cytomegalovirus infections. Classically, hyperpigmentation is associated with the disease, and intraoral pigmentation is perceived as the initial sign and develops earlier than the dermatological pigmentation. The symptoms of the disease usually progress slowly and an event of illness or accident can make the condition worse and may lead to a life threatening crisis. In this case, several oral as well as systemic manifestation of the Addison's disease was encountered.

Aetiology: Whereas primary adrenal insufficiency last century was most commonly due to tuberculosis, autoimmune disease currently accounts for most of the cases presenting outside of the newborn period. The various etiologies of Addison's disease can be grouped into three categories:

1) Adrenal dysgenesis
2) Adrenal destruction
3) Impaired steroidogenesis

Congenital adrenal hypoplasia (AHC), mutations of steroidogenic factor-1 (SF-1), and ACTH unresponsiveness can all lead to adrenal dysgenesis/hypoplasia, albeit the latter usually results in isolated deficiency of glucocorticoids. Autoimmune polyglandular syndrome (APS), adrenoleukodystrophy (ALD), adrenal hemorrhage, adrenal metastases, infections, and amyloidosis can all lead to destruction of adrenal gland.

Congenital adrenal hyperplasia (CAH), mitochondrial disorders, the Smith-Lemli-Opitz syndrome (SMOS), an enzyme deficiency in cholesterol metabolism, can all lead to impaired steroidogenesis. At birth, adrenal hemorrhage from anoxia/sepsis is most common, adrenal insufficiency from CAH usually presents in neonates, and in older children it often occurs as part of an autoimmune poly glandular syndrome or APS. In boys, adrenoleukodystrophy, DAX-1-related disorders are increasingly recognized, whereas adults have increasing incidences of infectious and metastatic adrenal failures.

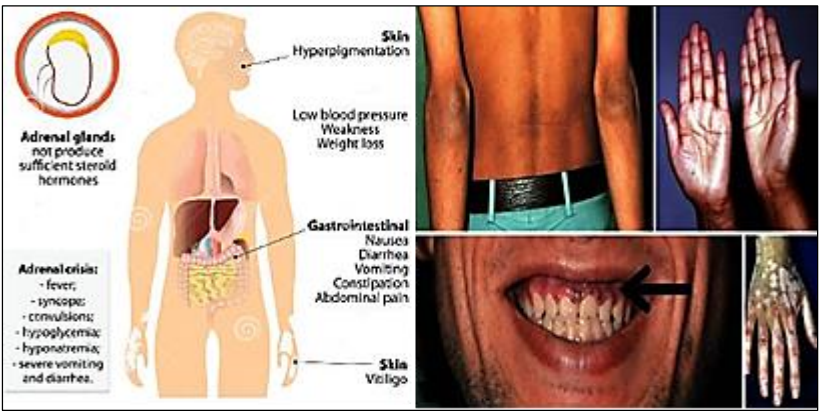


Fig 8: Addison's disease

Clinical features

Glucocorticoid insufficiencies are weight loss, malaise, anorexia, nausea, vomiting, gastrointestinal like diarrhoea or constipation, postural hypotension, hypoglycemia. Mineralocorticoid insufficiency is hypotension. Increased ACTH secretion are pigmentation occurs over sun exposed areas, pressure areas e.g. elbows, knees, palmar creases, knuckles, mucous membranes, conjunctivae, recent scars. Losses of adrenal androgen are

decrease in body hair, especially in female. In chronic presentation symptoms are chronic fatigue syndrome or depression and it is the pigmentation that commonly raises suspicion. The blood pressure may be normal with the patient lying down. Postural hypotension (i.e. a fall in systolic pressure of at least 20 mm Hg) is almost invariably present. Vitiligo is present in 10-20%.

Investigation

A morning serum cortisol level higher than 500 nmol/L (18 g/dL) usually excludes Addison disease, while a level below 165 nmol/L (6 g/dL) is suggestive of adrenal insufficiency. However, most patients will need a short synacthen test for confirmation or exclusion of Addison disease. This involves injecting 250 g of synacthen (tetracosactrin; synthetic analogue of adrenocorticotrophic hormone (ACTH]) intramuscularly or intravenously. Blood samples for serum cortisol are taken at 0, 30, and 60 minutes. An increase in serum cortisol level 30 or 60 minutes after the synacthen injection to above 500 nmol/L (18 g/dL) is considered a normal response, although the threshold cortisol level may vary according to local laboratory reference ranges. If the cortisol response to synacthen is inadequate, plasma ACTH level should be measured. A raised plasma ACTH level confirms the diagnosis of Addison disease, whereas patients with secondary adrenal insufficiency due to pituitary or hypothalamic disorders have a low or inappropriately normal plasma ACTH level. Plasma renin activity is elevated in Addison disease and is sometimes a useful investigation to distinguish between Addison disease and secondary adrenalinsufficiency.

Management

Patients with Addison's disease always need glucocorticoid replacement therapy and usually, but no always, mineralocorticoid. If the Addison's disease results from tuberculosis then this will need to be treated appropriately.

Chapter - 3

Diseases of the Gastroenterology

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a very common digestive disorder worldwide with an estimated prevalence of 18.1-27.8% in North America. Approximately half of all adults will report reflux symptoms at some time. It's defined as "Gastroesophageal reflux disease is a condition of troublesome symptoms and complications that result from the reflux of stomach contents into the esophagus". Diagnosis of Gastroesophageal reflux disease is typically based on classic symptoms and response to acid suppression after an empiric trial. Gastroesophageal reflux disease is an important health concern as it is associated with decreased quality of life and significant morbidity. Successful treatment of Gastroesophageal reflux disease symptoms has been associated with significant improvement in quality of life, including decreased physical pain, increased vitality, physical and social function, and emotional well-being. While Gastroesophageal reflux disease medications are not particularly expensive, the cost of treating Gastroesophageal reflux disease patients has been deemed 2-fold more costly than comparable individuals without Gastroesophageal refluxdisease.

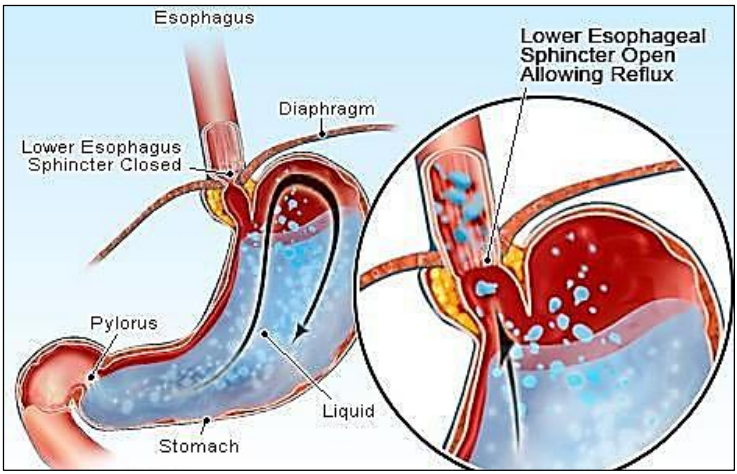


Fig 1: Gastroesophageal reflux disease

Etiology and Pathophysiology

Risk factors for Gastroesophageal reflux disease include older age, excessive body mass index (BMI), smoking, anxiety/depression, and less physical activity at work.Eating habits may also contribute to Gastroesophageal reflux disease, including the acidity of food, as well as size and timing of meals, particularly with respect to sleep. Recreational physical activity appears to be protective, except when performed post prandially. Gastroesophageal reflux is primarily a disorder of the lower esophageal sphincter (LES) but there are several factors that may contribute to its development. The factors influencing Gastroesophageal reflux disease are both physiologic and pathologic. The most common cause is transient lower esophageal sphincter relaxations (TLESRs). TLESRs are brief moments of lower esophageal sphincter tone inhibition that are independent of a swallow. While these are physiologic in nature, there is an increase in frequency in the postprandial phase and they contribute greatly to acid reflux in patients with Gastroesophageal reflux disease. Other factors include reduced lower esophageal sphincter (LES) pressure, hiatal hernias, impaired esophageal clearance, and delayed gastricemptying.

Clinical Features

Gastroesophageal reflux disease (GERD) is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung. Gastroesophageal reflux disease can be classified as non-erosive reflux disease (NERD) or erosive reflux disease (ERD) based on the presence or absence of esophageal mucosal damage seen on endoscopy. The following document will provide a brief overview of the epidemiology, clinical symptoms and complications of Gastroesophageal reflux disease as well as a more comprehensive review of the current approach to diagnosis and management.Typical symptoms are Acid regurgitation, heartburn,Epigastric fullness, epigastria pressure, epigastric pain, dyspepsia, nausea,bloating, belching (atypical symptoms). Extra oesophageal symptoms arechronic cough, bronchospasm, wheezing, hoarseness, sore throat, asthma, laryngitis, dentalerosions.

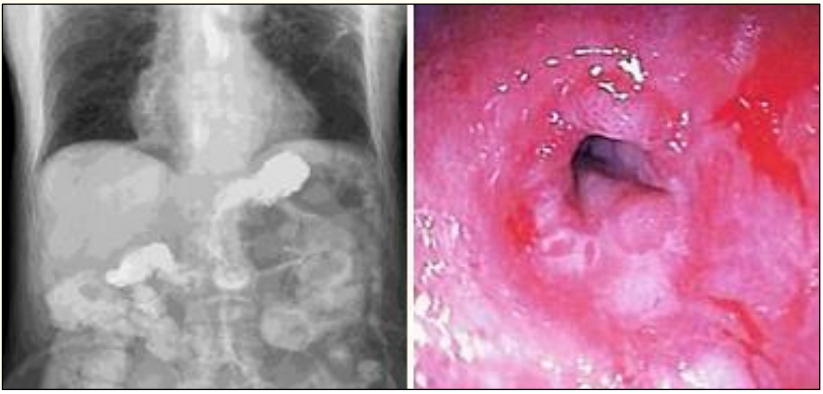


Fig 2: Barium esophagram and Upper endoscopy of Gastroesophageal reflux disease

- Complications
- Oesophagitis
- Barrett'soesophagus
- Anaemia
- Benign oesophageal stricture

Diagnosis

The diagnosis of Gastroesophageal reflux disease is typically made by a combination of clinical symptoms, response to acid suppression, as wellas objective testing with upper endoscopy and esophageal pH monitoring. For example, the combination of moderate to severe typical symptoms and endoscopic changes (erosive esophagitis or Barrett's esophagus) are highly specific (97%) for Gastroesophageal reflux disease (confirmed with pH testing). However, a well ken history alone can prove very valuable in the diagnosis, especially in the setting of heartburn and acid regurgitation which have a very high specificity (89% and 95%, respectively), albeit low sensitivity (38% and 6%) for Gastroesophagealreflux disease. This can allow one to make a presumptive diagnosis and begin empiric therapy, thereby avoiding a comprehensive and costly evaluation in every patient presenting with uncomplicated symptoms.

Ambulatory PH Monitoring

Ambulatory reflux monitoring is the only modality allowing direct measurement of esophageal acid exposure, reflux episode frequency and association between symptoms and reflux episodes. It is typically used to evaluate patients with persistent symptoms despite medical therapy,

particularly those without endoscopic evidence of Gastroesophageal reflux disease, in order to confirm the diagnosis. It can also be employed to monitor the control of reflux in those on therapy with persistent symptoms

Upper Endoscopy

Upper endoscopy is the primary modality used in the evaluation of the esophageal mucosa in patients with Gastroesophageal reflux disease and also allows for biopsies of concerning lesions (*e.g.*, Barrett's metaplasia, strictures or masses). It is important though to understand that there are limitations with the use of upper endoscopy in the diagnosis of Gastroesophageal reflux disease. For instance, while an endoscopy showing esophagitis or Barrett's esophagus essentially confirms the diagnosis of Gastroesophageal reflux disease (high specificity), a normal endoscopy does not refute the diagnosis. In fact, most patients with typical symptoms of Gastroesophageal reflux disease will have no endoscopic evidence of Gastroesophageal reflux disease on esophagogastroduodenoscopy.

Barium Esophagram

Barium esophagram was once recommended as a screening test for Gastroesophageal reflux disease, but is no longer part of the diagnostic evaluation. A 1996 study of 125 patients compared barium esophagram to esophageal pH monitoring to assess the accuracy of barium screening as a predictor of abnormal esophageal acid exposure. A significantly greater degree of abnormal esophageal acid exposure occurred in patients who had a hiatal hernia or spontaneous reflux on bariumradiography.

However, the sensitivity and specificity of barium radiography for abnormal degrees of acid reflux were insufficient and therefore this test is no longer recommended in the diagnosis of Gastroesophageal reflux disease.

Esophageal Manometry

Esophageal manometry is most useful for the evaluation of dysmotility and has only limited utility in the evaluation of Gastroesophageal reflux disease [13]. Gastroesophageal reflux disease is a chronic disease that typically requires long term management in the form of lifestyle modification, medical therapy and, for a subset of patients, surgical therapy and constitutional homeopathic treatment.

Achalasia Cardia

Neuromuscular motility disorder of oeophagus due to degeneration of Auerbach's plexus causing muscular hypertrophy and impaired oesophageal emptying and characterized by dysphagia and regurgitation offood.

Causes: Exact cause is unknown. But more in female when compared to males.

Clinical Features: Dysphagia, food is retained for hours, food is foul smelling, sensation of food sticking, can pinpoint site of obstruction, initially difficulty in swallowing liquids, less marked with solids, substernal discomfort and worse by after fast eating or drinking,better by coldwater.

Diagnosis

Barium meal examination: Dilation and elongation of esophagus, upper part of barium is horizontal and lower part shows smooth, pointed end. Endoscopy can show the dilation of oesophagus.

Management

To prevent regurgitation-avoid lying down one to two hours after meals, avoid straining and coughing, avoid wearing tight corsets.

Gastritis

Gastritis is a histological diagnosis, although it can sometimes be recognized at endoscopy.

Acute Gastritis

It is often erosive and hemorrhagic. Neutrophils are the predominant inflammatory cell in the superficial epithelium. Many cases result from aspirin or NSAID ingestion.

Acute gastritis often produces no symptoms but may cause dyspepsia, anorexia, nausea or vomiting, haematemesis or melaena. Treatment should be directed to the underlying cause. Short term symptomatic therapy with antacids, acid suppression or antiemetic, homoeopathic medicines may be necessary.

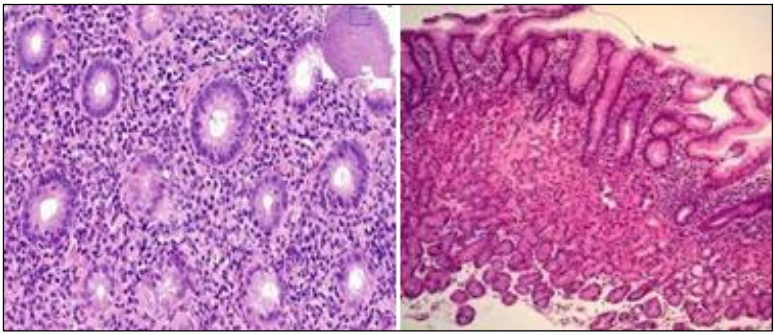


Fig 3: Histopathology of Chronic gastritis

Chronic Gastritis

The most common cause of chronic gastritis is H. Pylori. The predominant inflammatory cells are lymphocytes and plasma cells. Correlation between symptoms and endoscopic or pathological findings I spoor. Most patients are asymptomatic and do ot require any treatment. Socioeconomics and environmental hygiene are inevitably the most important background factors in transmission of *H. pylori* infection worldwide, these socioeconomic factors being, thereby, the background factors also in epidemiology of chronic gastritis and its sequelae. The infection rate in childhood and the age-specific prevalence of *H. pylori* gastritis are high in the "old" birth cohorts born decades earlier than the prevalence in the "young" birth cohorts born more recently and in whom the infection rate of *H. pylori* at childhood is low. Thus, the mean prevalence of gastritis at the population level reflects the average of the prevalence of chronic gastritis in different birth cohorts, and the mean rate of *H. pylori* infection at pediatricage.

Peptic Ulcer Disease

The term peptic ulcer refers to an ulcer in the lower oesophagus, stomach or duodenum in the jejunum after surgical anastomosis to the stomach, or, rarely in the ileum adjacent to a meckel's diverticulum.

Ulcer in the stomach or duodenum may be acute or chronic: both penetrate the muscularis mucosae but the acute ulcer shows no evidence offibrosis.

Etiology

Peptic ulcer disease includes both gastric and duodenal ulcerswhich posed a major threat to the world's population over the past two centuries with a high morbidity and mortality. The evolution of knowledge regarding etiopathogenesis of peptic acid disease from acid-driven disease to an infectious disease has opened up this topic for various studies to find the best possible options for management of this disease. The discoveryof *Helicobacter pylori* has evinced great interest in the role played by this microbe. The eradication of this organism has been found to be of paramount importance to minimize the complications of peptic ulcers. The management of peptic ulcer disease and its complications remain a challenge. In addition, non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, smoking, excessive alcohol use, emotional stress and psychosocial factors are increasingly important causes of ulcers and their complications even in *H. pylori* negative patients. Other rare causes of peptic ulcer disease in the

absence of *H. pylori,* NSAIDs, and aspirin also exist. Epidemiological studies reveal a very strong association between *H. pylori* infection and peptic ulcer disease. More than half the world's population has a chronic *H. pylori* infection of thegastroduodenal mucosa, yet only 5-10% develops ulcers. Factors that determine whether the infection will produce the disease depends on the pattern of histological changes, gastritis induced changes in homeostasis of gastric hormones and acid secretion, gastric metaplasia in the duodenum, interaction of *H. pylori* with the mucosal barrier, immunopathogenesis, ulcerogenic strains, and genetic factors. Management of peptic acid disease varies from using H_2 receptor antagonist, proton pump inhibitors (PPI) to triple chemotherapy and sequential regimen for *H. pylori*. Similarly treating perforation varies from a conservative non operative approach to a surgicalapproach.

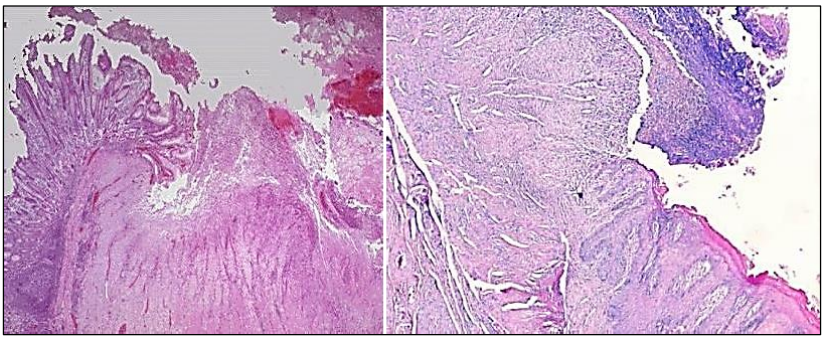


Fig 4: Histopathology of peptic ulcer

Pathology

Chronic gastric ulcer is usually single, 90% are situated on the lesser curve within the antrum or at the junction between body and antral mucosa. Chronic duodenal ulcer usually occurs in the first part of the duodenum just distal to the junction of pyloric and duodenal mucosa, 50% are on the anterior wall. Gastric and duodenal ulcers coexist in 10% of patients and more than one peptic ulcer is found in 10-15% ofpatients.

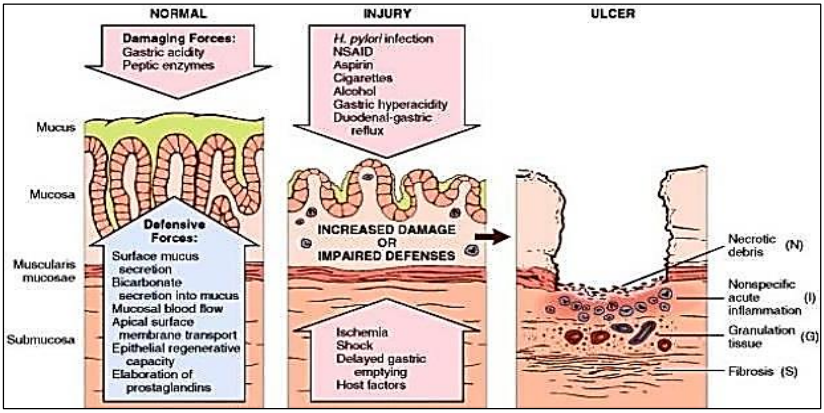


Fig 5: Pathophysiology of Peptic ulcer

A chronic ulcer extends to below the muscularis mucosa and the histology shows four layers: surface debris, an infiltrate of neutrophils, granulation tissue and collagen.

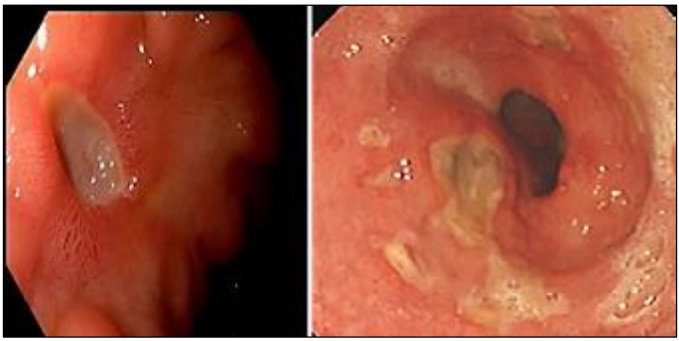


Fig 6: Endoscopy of peptic ulcer

Clinical Features

Peptic ulcer disease is a chronic condition with a natural history of spontaneous relapse and remission lasting for decades.

Pain is referred to the epigastrium and is often so sharply localized that the patient can indicate its site with two or three fingers (the pointing sign). Hunger pain occurs intermittently during the day, often when the stomach is empty. Pain wakes the patients from sleep and may be relieved by food, a drink of milk or antacids; this symptoms is very characteristic of duodenal ulcer. Pain is ameliorated by food, milk and by belching and vomiting. Relief by vomiting is more typical of gastric ulcer than of duodenal ulcer. Periodicity pain present and last for several weeks at a time. Between

episodes the patient feels perfectly well. Other symptoms that occur, especially during episodes of pain, include water brush, heartburn, loss of appetite and vomiting. Persistent vomiting occurring daily suggests gastric outletobstruction.

Investigation

The diagnosis can be made by double contrast barium meal examination or by endoscopy. Endoscopy is the preferred investigation because it is more accurate and has the enormous advantage that suspicious lesions and HP status can be evaluated bybiopsy.

Complication

- Perforation
- Gastric outletobstruction
- Bleeding

Management

Cigarette smoking, aspirin and NSAIDs should be avoided. Alcohol in moderation is not harmful and no special dietary advice is required, but to avoid very spicy food. All patients with proven acute or chronic duodenal ulcer disease and those with gastric ulcer who are helicobacter pylori positive should be offered eradication therapy as primary therapy. Treatment is based upon a proton pump inhibitor taken simultaneously with 2 antibiotics for one week and along with homoeopathic treatment.

Tropical Sprue

Intestinal malabsorption syndrome characterized by steatorrhea, glossitis, stomatitis, abdominal distention and weight loss.

Etiology

Prolong residence in hills, chronic dysentery, fatigue, excessive fatty diet.

Clinical Features

Diarrhoea is persistent frequently worse by morning, stools are pale, frothy, bulky, extremely offensive, steatorrhoea, float on water, anorexia, sore mouth, weakness, irritability, loss of weight. Signs are pulse is fast, weak, anaemia moderate to severe, cheilosis, angular stomatitis, abdomen distention, doughy feel.

Diagnosis

Barium meal x ray of small intestine can find out altered mucosal pattern, intestinal dilation, clumped, scattered barium.

Management

Adequate physical and mental rest, control diarrhoea with anti-diarrhea drugs, low roughage diet.

Inflammatory Bowel Disease

Ulcerative colitis and crohn's disease are chronic inflammatory bowel disease which pursues a protracted relapsing and remitting course, usually extending over years. The incidence of inflammatory bowel disease (IBD) varies widely between populations: Crohns disease appears to be very rare in the underdeveloped world yet ulcerative colitis, although still unusual, is becoming morecommon.

Ulcerative Colitis

Ulcerative colitis (UC) is a chronic disease with recurrent uncontrolled inflammation of the colon. The rectum is always affected with inflammation spreading from the distal to the proximal colonic segments. The terminal ileum is typically not involved but some patients with extensive disease may show endoscopic signs of "backwash ileitis". As the course of disease and extent vary considerably among patients, an individualized diagnostic and therapeutic approach isnecessary.

Fig 7: Ulcerative colitis

Only a minority of patients have chronic, unremitting symptoms. Emotional stress, intercurrent infection, gastroenteritis, antibiotics or NSAID therapy may provoke a relapse. Rectal bleeding and mucus discharge. Sometime accompanied by tenesmus.

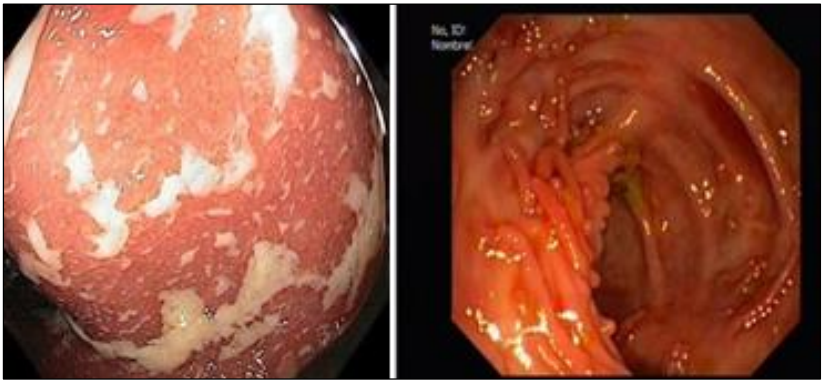


Fig 8: Endoscopy of ulcerative colitis

The disease remains confined to the rectum in approximately 25% of cases, and in the remainder of cases, ulcerative colitis spreads proximally and contiguously. Pancolitis occurs in 10% of patients. The distal terminal ileum may become inflamed in a superficial manner, referred to as backwash ileitis. Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As ulcerative colitis becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead pipe appearance observed on bariumenema.

Clinical Features

Some patients pass frequent, small volume fluid stools, while other are constipated and pass pellet stools. Weight loss, malaise, anorexia and abdominal pain occur and the patient is toxic with fever.

Complications

- Severe, life threatening inflammatory of thecolon
- Perforation of the small intestine orcolon
- Life threatening acute haemorrhage
- Fistula and perianaldisease
- Cancer
- Seronegativearthritis
- Erythema nodosum, pyoderma gangrenosum, oral aphthous ulcers, conjunctivitis, iritis, primary sclerosing cholangitis, gall stones, fatty liver, portal pyaemia, liver abscess, amyloidosis, oxalate calculi, deep vein thrombosis, portal or mesenteric veinthrombosis.

Investigations

Blood tests are like complete blood test, vit B12, ESR, serum albumin etc., Bacteriology like stool cultures are performed to exclude superimposed enteric infection in patients who present with exacerbations of inflammatory bowel disease. Sigmoidoscopy, barium studies, plain radiographs and radionuclidescans.

Management

Drug treatment, nutritional therapy, surgical treatment and homoeopathic medicines.

Crohns Disease

The sites most commonly involved in order of frequency are terminal ileum and right side of colon, colon alone, terminal ileum alone, ileum and jejunum. Characterized, the entire wall of the bowel is oedematous and thickened. There are deep ulcers which often appear as linear fissures, thus the mucosa between them is described as cobblestone. Deep ulcer may penetrate through the bowel wall to imitate abscesses orfistulae.

Its prevalence has continually increased over the past 50 years with the highest incidence being reported in northern Europe, the United Kingdom and North America.

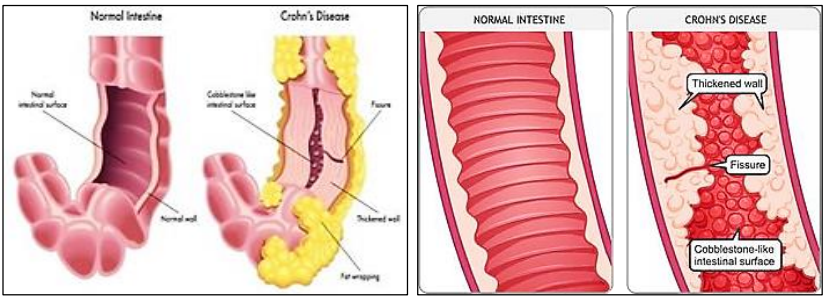


Fig 9: Crohns disease

Fistula may develop between adjacent loops of bowel or between affected segmens of bowel and the bladder, uterus or vagina and may appear in the perineum. Characteristically, the changes are patchy. Even when a relatively short segment of bowel is affected, the inflammatory process is interrupted by islands of normal mucosa and the change from the affected part is abrupt. A small lesion separated in this way from a major area of involvement is referred to as a “skip” lesion. The mesenteric lymph nodes are enlarged and the mesentery thickened. Histologically, chronic

inflammation is seen through all the layer of the bowel wall, which is thickened as a result. There are focal aggregates of epithelioid histiocytes, which may be surrounded by lymphocytes and contain giant cells. Lymphoid aggregates or microgranulomas are also seen, and when these are near to the surface of the mucosa they often ulcerate to form tiny aphthous like ulcers.

Clinical Features

Chronic diarrhoea, defined as a decrease in faecal consistency for more than 4 weeks, is the most common presenting symptom. Abdominal pain (70%), weight loss (60%) and blood, mucus or both in stools (40-50%) are also common findings in Crohns disease. Extraintestinal manifestations affect approximately a third of patients with inflammatory bowel disease. The most commonly observed extraintestinal manifestation is primary peripheral arthritis (33%); aphthous stomatitis, uveitis, erythema nodosum and ankylosing spondylitis can be seen whilst pyoderma gangrenosum, psoriasis and primary sclerosing cholangitis are relatively uncommon. Fistulae, a complication of Crohns disease, occurs in up to 35% of patients with Crohns disease, with perianal fistula occurring in 20%.

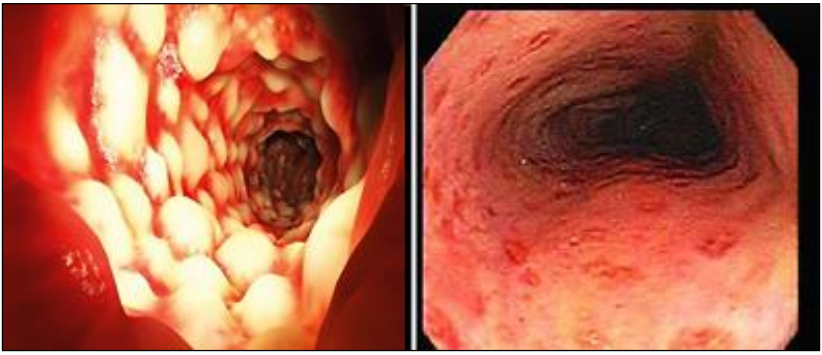


Fig 10: Endoscopy of Crohns disease

Risk Factors

Crohns disease has a peak age prevalence of 30-39 years old and gender influence differs in various demographics. In a Canadian and New Zealand population, females are 10-30% more likely to acquire the disease than males. Other inflammatory diseases have been implicated with Crohns disease including asthma, psoriasis, pericarditis, ankylosing spondylitis, atopic dermatitis and primary sclerosing cholangitis. Their impact tends to be most influential duringchildhood.

Different Diagnosis

Other cases of right iliac fossa mass: caecal carcinoma, appendix abscess, infection (tuberculosis, yersinia, actinomycosis), mesenteric adenitis, pelvic inflammatory disease, lymphoma.

Management

Intravenous fluids, antibiotics for proven infection, nutritional support, avoidance of opiates, antidiarrheal agents and homoeopathic management.

Coeliac Disease

Gluten sensitive intestinal malabsorption syndrome characterized by steatorrhea, rapid weight loss and growth retardation.

Causes: etiology is unknown, evidence pints towards gluten sensitivity.

Clinical Features

Diarrhoea is persistent, frequent passage of stools by morning. Stools are pale, frothy, bulky, extremely offensive, steatorrhoea. Signs are fever slightly raised, hypotension, pallor, weak and emaciated.

Diagnosis

In barium meal x ray can find loss of mucosal patter of small intestine, intestinal dilation, clumped, scattered barium.

Management

Control of diarrhoea with anti diarrhoea drugs and gluten free diet, low roughagediet.

Diverticulitis

Inflammation of diverticulum called diverticulitis. It is commonly occurring in sigmoid and descending colon and characterized by lower abdominal colicky pain, with increasing constipation.

Causes: Due to atrophy of muscular coat of colon, obesity, faecolith (obstruction of diverticulum).

Clinical Features

Pain in abdomen especially left iliac fossa, discomfort, gradually increasing in severity and frequency, worse by pressure, tight clothing, better by after defecation, passing flatus, nausea, vomiting, stools are small, hard, frequent, flatulence, abdominal distension, low grade fever. Signs are localized tenderness in left iliac fossa, muscle guarding.

Diagnosis

Barium enema examination, diverticula clearly visualized after barium evacuation.

Management

High fiber diet, avoid constipation, physical as well as mental rest.

Chapter - 4

Diseases of the Nephrology

Glomerulonephritis

Glomerulonephritis (GN) means “inflammation of glomeruli”. It excludes glomerular diseases without cell proliferation or nephritic presentations, such as minimal change disease, membranous nephropathy, and focal segmental glomerulosclerosis that can, none the less, chronically compromise renal function. In primary glomerulonephritis, disease is almost entirely restricted to the kidneys (as in IgA nephropathy or post streptococcal glomerulonephritis) while in secondary glomerulonephritisit occurs in association with more diffuse inflammation (as in systemic lupus erythematosus or systemic vasculitis). Prompt diagnosis of glomerulonephritis is vital as patients with even mildly impaired renal function, hypertension, and urinary abnormalities may rapidly lose kidney function if not treatedurgently.

Nearly 200 years ago, Richard Bright first described glomerular disease, diagnosing proteinuria in his patients by using a candle to heat urine on a spoon to determine whether it precipitated with heat.Bright also first recognized the relationship of scarlatina (due to streptococcal infection) to subsequent glomerulonephritis in the 1800s. With the advent of immunopathology, studies of serum sickness models in rabbits by Germuth and Dixon provided seminal insights into the immune mechanisms that underlie most forms ofglomerulonephritis.

Causes

Causes of glomerulonephritis are systemic vasculitis, SLE, good pasture’s (anti GBM) disease, aggressive phase of other inflammatory nephritis, viral infection, bacterial endocarditis, Lupus.

Types of Glomerulonephritis

Post Infectious Endocapillary Glomerulonephritis

Post streptococcal glomerulonephritis is the best known example of endocapillary glomerulonephritis, the most common form of acute

glomerulonephritis seen after some bacterial, viral, fungal, and parasitic infections. Although this pattern of glomerular injury after a streptococcal infection remains an important cause of acute renal failure in the developing world.

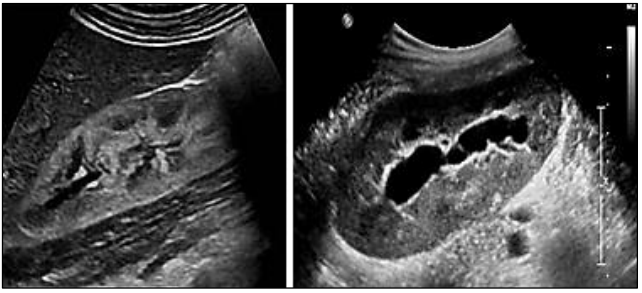


Fig 1: Glomerulonephritis ultrasound

Mesangioproliferative Glomerulonephritis/IgA Nephropathy

IgA nephropathy is the commonest of all glomerulonephritisworldwide. Thus although only 4%-13% of patients present with acute nephritis. 9 Peak presentation is during the second and third decades showing a 2:1 male preponderance with attacks sometimes after infection. IgA nephropathy is the classic mesangioproliferative glomerulonephritis where cellular proliferation may be either diffuse or focal but affects predominantly the mesangium. Immunofluorescence shows para mesangial deposition of IgA (with some IgG and IgM) together with alternative pathway complement components, while electron microscopy shows mesangial dense deposits. Polymeric IgA1 is deposited in the kidney after overproduction of systemic IgA1 polymers (possibly in response to infection) together with impaired clearance through both the hepatic and the myeloidroutes.

In addition abnormal glycosylation of IgA may make it more prone to self-aggregate and form immune complexes with affinity for the mesangium.

The disease is associated with a raised serum concentrations of IgA in 50% of patients, but serum complement levels are normal as complement activation is restricted to the kidneysalone.

Henoch Schonlein Purpura

However, as a small vessel vasculitis, HSP also has the systemic features of a purpuric rash largely affecting the lower limbs, arthritis or arthralgia, and abdominal pain sometimes in association with rectal bleeding.The disease is most commonly seen in those less than 20 years of age.

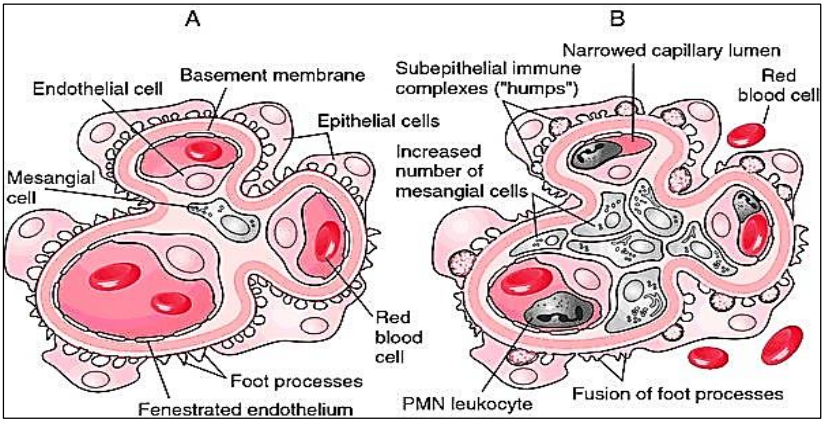
Rapidly Progressive Glomerulonephritis

The rapidly progressive glomerulonephritis are the most serious of all glomerulonephritis with the potential to destroy renal function within days. Although causes are heterogeneous, they are united by the histological finding of extensive crescents (a proliferation of parietal epithelial cells and mononuclear phagocytes with possible fibroblasts in Bowman's capsule) affecting more than 50% of glomeruli. Causes fall into three broad categories with different presentations, treatments, and prognoses. Biopsy shows a focal or diffuse proliferative glomerulonephritis with extensive crescents. The pathogenesis of vasculitis remains the focus of much research but direct immunoglobulin deposition in the glomerulus is not thought to play a significant part (hence the term pauci-immune). Serologically, however, these diseases are linked in about 90% of cases by the finding of antineutrophil cytoplasmic antibodies (ANCA).

Antibody staining is usually directed against the neutrophil cytoplasm in Wegener's with an antigen specificity for proteinase 3 on ELISA, whereas in microscopic polyangiitis it is generally perinuclear in pattern and is directed against myeloperoxidase. A direct causative role for ANCA in small vessel vasculitis remains controversial with experimental evidence pointing towards roles for neutrophils, macrophages, and T-cells in itspathogenesis.

Membranoproliferative Glomerulonephritis

This rare form of glomerulonephritis has enjoyed renewed interest after the discovery that a subtype of MCGN type I is associated with chronic hepatitis C infection. MCGN commonly presents as a nephrotic syndrome but in 16%-30% of patients the initial presentation is with acute nephritis. The disease can be subdivided into types I and II, with its idiopathic forms mostly seen in children and young adults with cases presenting at a younger age in type II than in type I disease, with a slight female preponderance. Type I MCGN shares some features with lupus nephritis, and a similar histological picture can also be seen with endocarditis and infected arteriovenous shunts. In type II MCGN, patients may have an associated partial lipodystrophy giving them a very gaunt facial appearance.



A. Normal **B. Abnormal**

Fig 2: Glomerulonephritis

Lupus Nephritis

Renal involvement in systemic lupus erythematosus can present with proteinuria, haematuria, nephrotic syndrome, or with an acute nephritis. It is rarely the first manifestation of systemic lupus but usually occurs within five years and may be the first presentation leading to a definitive diagnosis.24 Patients (most commonly women in their 20s and 30s with a black preponderance) will frequently have suffered lethargy, arthralgia or arthritis, skin rashes, and the symptoms of pleurisy and pericarditis in the months before presentation.

25 More than any other glomerulonephritis, lupus nephritis can change and evolve over time so that in a patient with an initially benign glomerular lesion, a new presentation with acute glomerulonephritis should prompt repeat biopsy and if needed more aggressive treatment. High titres of antinuclear antibodies and anti-double stranded DNA antibodies together with low complement levels are helpful in a nephritic flare, although changes in such markers often precede the actual glomerular inflammation, sometimes bymonths.

Clinical Features

Clinical features of glomerulonephritis are pink or cola coloured urine from red blood cells in urine, foamy urine due to excess protein (proteinuria), swelling evident in face, hand, feet and abdomen and hypertension.

Renal Calculi

Formation of stone in any part of urinary tract.

Causes: decrease fluid intake, chronic diarrhoea, urinary tract obstruction, recurrent urinary tract infection, polycystic kidney disease, vitamin D toxicity, excessive intake of calcium, hyperoxaluria, crohn's disease, gout, myeloproliferative disorders, excessive intake of oxalate.

Clinical Features

Pain in renal region, nausea and vomiting, sudden onset of pain, pain starts from loin and radiates to down wards forwards towards to knee and rolls, strangury, haematuria, pain worse by movement, changing position, walking up stairs. Sign is tenderness of renalangle.

Complications

Impaction and obstruction, stricture of ureter, anuria.

Diagnosis

Macroscopic for blood, pus, sediments in urine. Microscopic also can find RBC's and pus cells. In radio opaque calculi in x ray KUB, Ultra sound abdomen can found calculi more than 1 cm cast a specific shadow.

Management

Plenty of fluids, control and treatment of infection.To remove stone and prevent complications.

Renal Failure

Renal failure is failure of the excretory function of the kidneys, leading to retention of nitrogenous waste products of metabolism. Sudden and usually reversible loss of renal function, which develops over a period of days or weeks. An increase in plasma Creatinine concentration to more than 200 micro mol/l is often used as the biochemicaldefinition.

Causes

Causes of renal failure are pre renal, intrinsic renal, post renal and systemicdiseases.

Pre renal are systemic (heart failure, shock), local (renal artery occlusion/stenosis, diseases affecting arterioles), intrinsic renal are acute tubular necrosis/toxic/septic renal failure, glomerular disease-primary component of systemic disease, interstitial disease, in post renal are stones, inflammation, tumor, in systemic diseases are acting via one or more of these three categories.

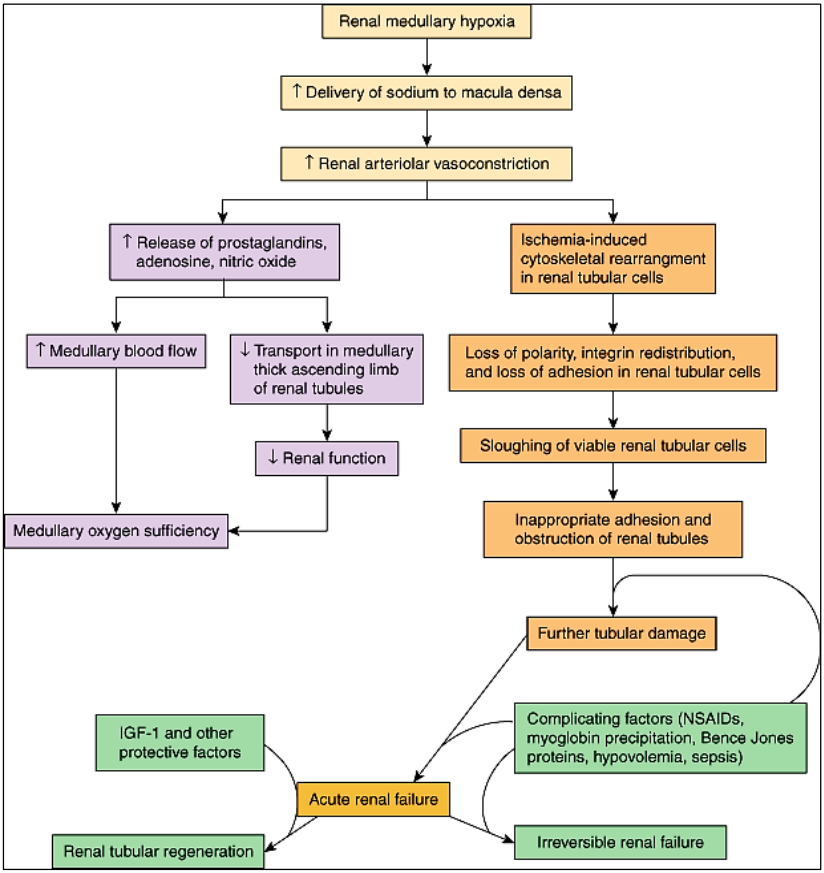


Fig 3: Pathogenesis of renal failure

Clinical Features

Decreased urinary sodium concentration especially in septic patients. Decreased urine output, although occasionally urine output remains normal, fluid retention, causing swelling in your legs, ankles or feet, Shortness of breath, fatigue, confusion, nausea, weakness, irregular heartbeat.

Chronic Renal Failure

Chronic kidney disease (CKD) is recognized as a major health problem affecting approximately 13% of the United States population. Numbers of prevalent CKD patients will continue to rise, reflecting the growing elderly population and increasing numbers of patients with diabetes and hypertension. As numbers of CKD patients increase, primary care practitioners will be confronted with management of the complex medical

problems unique to patients with chronic renal impairment. As well documented in the literature, the nephrologist rarely manages the medical needs of CKD patients until renal replacement therapy is required. In this chapter we will define CKD staging and discuss five complications associated with CKD: anemia, hyperlipidemia, nutrition, osteodystrophy, and cardiovascularrisk.

Classification ofCKD

- **Stage 1:** normal eGFR ≥ 90 mL/min per 1.73 m^2 and persistent albuminuria
- **Stage 2:** eGFR between 60 to 89 mL/min per 1.73m^2
- **Stage 3:** eGFR between 30 to 59 mL/min per 1.73m^2
- **Stage 4:** eGFR between 15 to 29 mL/min per 1.73m^2
- **Stage 5:**eGFR of < 15 mL/min per 1.73 m^2 or end stage renal disease

While anemia in CKD can result from multiple mechanisms (iron, folate, or vitamin B12 deficiency; gastrointestinal bleeding; severe hyperparathyroidism, systemic inflammation, and shortened red blood cell survival).

Decreased erythropoietin synthesis is the most important and specific etiology causing CKD associated anemia. Erythropoietin is a glycoprotein secreted by the kidney interstitial fibroblast and is essential for the growth and differentiation of red blood cells in the bone marrow. In CKD, tubular atrophy generates tubulointerstitial fibrosis, which compromises renal erythropoietin synthetic capacity and results in anemia. The anemia of CKD increases morbidity and mortality from cardiovascularcomplications (angina, left ventricular hypertrophy (LVH) and worsening heart failure). The term "CKD-associated mineral and bone disorders" comprises abnormalities in bone and mineral metabolism and/or extra- skeletal calcification secondary to CKD pathophysiology. Renal osteodystrophy is the spectrum of histological changes, which occur in bone architecture of patients with CKD. The kidney is the primary site for phosphate excretion and 1-α-hydroxylation of vitamin D. CKD patients develop hyperphosphatemia as a result of inadequate 1, 25 dihydroxy-vitamin D levels that reflect reduced synthesis from parenchymalscarring.

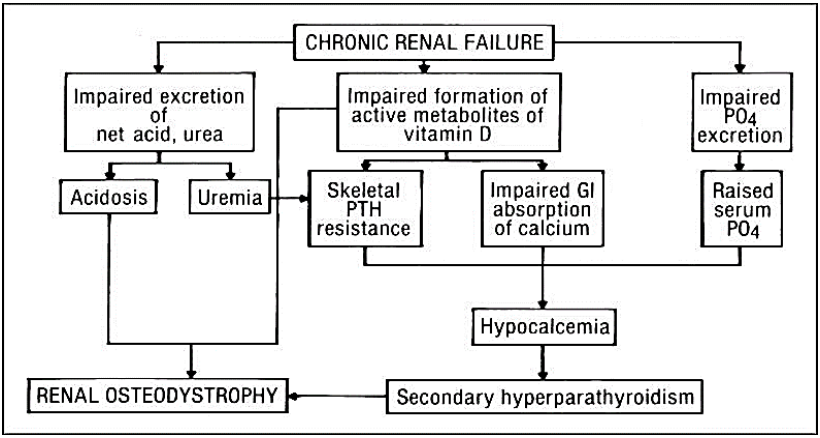


Fig 4: Chronic Renal Failure

Hypertension is a traditional cardiovascular risk factor which contributes to the cardiovascular risk associated with CKD. Szcech and colleagues demonstrated that patients with hypertension are at increased risk for new or recurrent cardiovascular events in individuals with stage 2-3 CKD. CKD patients are more likely to develop congestive heart failure (CHF). Bibbins *et al*. evaluated the association between CKD and new-onset CHF in African and Caucasians Americans.

Dyslipidemia is a major risk factor for cardiovascular morbidity and mortality and is common among patients with CKD. As patients progress through the stages of CKD, nutritional requirements are altered and metabolism of protein, water, salt, potassium, and phosphorous are affected.

Urethritis

Inflammation of urethra characterized by dysuria, thick, purulent discharge per urethra.

Causes: gonococcal urethritis-neisseriagonorrhea, Chlamydia trachomatis, STD.

Clinical Features

Severe scalding pain on urination, frequent urination, urgency to pass urine, burning during micturition, fever, headache, malaise, thick and greenish yellow purulent discharge. Signs are fast pulse, temperature more than 100 degree C, lymph nodes enlarged, external urethral meatus red, swollen.

Complications

Chronic cervicitis, infertility, bartholinitis.

Diagnosis

Gram stained urethral discharge.

Management

Improvement of general health, antibiotics, simultaneous treatment of sexualpartner.

Nephrotic Syndrome

When substantial amount of protein are lost in the urine, a series of secondary phenomena occur. Evidence of fluid retention or oedema and more than 3.5 g of proteinuria per day. The disease that cause nephritic syndrome always affect the glomerulus and tend to be non-inflammatory or subacute examples of inflammatoryglomerulonephritis.

It is caused by increased permeability through the damaged basement membrane in the renal glomerulus especially infectious or thromboembolic. It is the result of an abnormality of glomerular permeability that may be primary with a disease specific to the kidneys or secondary to congenital infections, diabetes, systemic lupus erythematosus, neoplasia, or certain drug use. Nephrotic syndrome is an important chronic disease in children. The estimated annual incidence of nephrotic syndrome in healthy children is two to seven new cases per 100,000 children younger than 18 years of age. More common in boys than girls in younger age groups, but once adolescence is reached there is no significant difference between genders. Increased incidence and more severe disease seen in African American and Hispanicpopulations.

Causes

Primary Cause: Minimal change nephropathy, focal glomerulosclerosis, membranous nephropathy, hereditary nephropathies. Non inflammatory glomerulonephritis-minimal change nephropathy, focal and segmental glomerulosclerosis (FSGS), membranous nephropathy, proliferative/inflammatory glomerulonephritis-mesangiocapillary glomerulonephritis (MCGN), subacute proliferative nephritis, systemic lupus erythematosus (SLE), diabetic nephropathy andamyloidosis.

Infection: HIV, hepatitis B virus, human immunodeficiency virus, hepatitis C, cytomegalovirus, toxoplasmosis, parvovirus B1, amyloidosis and paraproteinemias, preeclampsia.

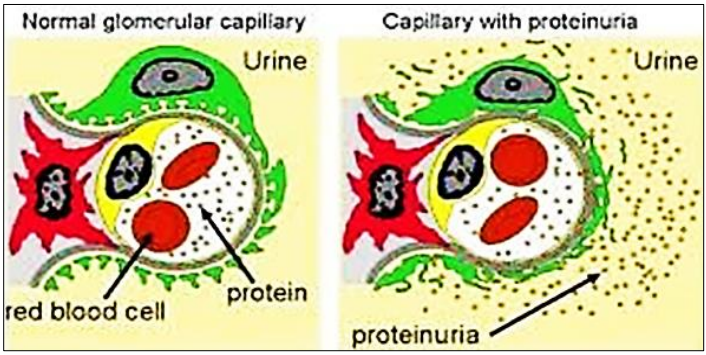


Fig 5: Nephrotic syndrome

Pathophysiology

The glomerular capillaries are lined by a fenestrated endothelium that sits on the glomerular basement membrane, which in turn is covered by glomerular epithelium, or podocytes, which envelops the capillaries with cellular extensions called foot processes, these processes interdigitate with special cell junctions called the slit diaphragm which together forms the glomerular filter. Normally, larger proteins (greater than 69 kD) are excluded from filtration. Destruction of podocytes above a critical mass also leads to irreversible glomerular damage. Proteinuria that is more than 85% albumin is selective proteinuria. Albumin has a net negative charge, and it is proposed that loss of glomerular membrane negative charges could be important in causing albuminuria. Nonselective proteinuria, being a glomerular leakage of all plasma proteins, would not involve changes in glomerular net charge but rather a generalized defect in permeability.

Mutations in several podocyte proteins have been identified in families with inherited nephrotic syndrome; a plasma factor may alter glomerular permeability, especially in patients with the steroid-resistant nephrotic syndrome and lastly altered T-lymphocyte polarized immune responses, in that the T-cells could result in the production of a permeability factor. Increased plasma levels of IgE, IgG4, and association with atopy suggest type II cytokine bias in patients with MCNS. *In vitro* studies suggest that podocytes express receptors for IL-4 and IL-13, the activation of these receptors might disrupt glomerular permeability resulting in proteinuria. No particular cytokine triggers the nephrotic syndrome. Many of the complications of nephrotic syndrome can be linked to dysregulated lipid metabolism and dyslipidemia. These abnormalities include elevated plasma levels of cholesterol, triglycerides, and the apolipoprotein B; decreased

lipoprotein lipase activity in the endothelium, muscle and adipose tissues; decreased hepatic lipaseactivity, and increased levels of the enzyme PCSK9. Also, there is an increase in the plasma levels of immature HDL particles and reduced cholesterolefflux.

Clinical Features

Clinical features of nephrotic syndromes are oedema accumulates predominantly in the lower limb in adults, extending to the genitalia and lower abdomen as it gets more severe. In morning, the upper limbs and face may be more affected. In children, ascites occurs early and oedema is often seen only in the face. Blood volume may be normal, reduced or increased.

Investigation

Urine Test: Urine samples over 24 hours (for an accurate measure), proteinuria (3 g protein) is diagnostic. Lipiduria, the presence of free lipid or lipid within tubular cells, within casts, or as free globules, suggests a glomerular disorder.

Blood Tests: The serum albumin level is classically low in nephrotic syndrome, serum albumin often is < 2.5 g/dL.

Creatinine concentrations vary by degree of renal impairment. Total cholesterol and triglyceride levels are typically increased. Serologic studies: The role of testing for secondary causes of nephrotic syndrome.

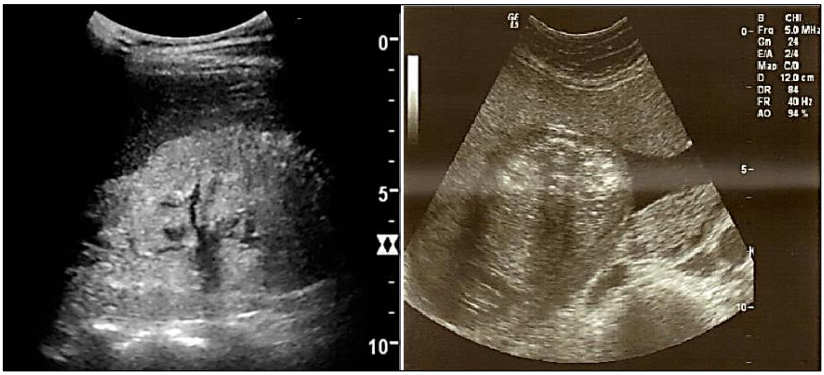


Fig 6: Nephrotic syndrome ultrasonography

Ultrasonographic: Individuals with a single kidney may be prone to developing focal glomerulosclerosis, having only one kidney is also a relative contraindication to kidney biopsy.

Ultrasonography also demonstrates renal echogenicity. Increased renal echogenicity is consistent with intrarenal fibrosis

Renal Biopsy

Indicated for the following: congenital nephrotic syndrome, children older than 8 years at onset, steroid resistance, frequent relapses or steroid dependency, significant nephritic manifestations.

Different Diagnosis

The differential diagnosis includes:

- **Hepatic:** Insufficiency, hepatocellular cirrhosis, Budd-Chiari syndrome
- **Digestive:** Exudative enteropathy, lymphangiectasia, malnutrition
- **Cardiac:** Hereditary angioneuroticedema
- **Immune:** Anaphylaxis
- Complications
- Generalized edema
- Respiratorydistress
- Sepsis
- Peritonitis
- Thromboembolism
- Failure to thrive

Patient Education

Advise to take low salt diet intake.

Interstitial Nephritis

It is divided in to acute and chronic interstitial nephritis.

Acute Interstitial Nephritis: It is refers to acute inflammation within the tubule interstitium. Acute interstitial nephritis (AIN) is an under recognized and under diagnosed cause of acute kidney injury (AKI). It is estimated to account for 15-20% of cases of AKI; it is the reported diagnosis in 2.8% of all kidney biopsies, and 13.5% of biopsies done specifically for acute renal failure. Considerable evidence implicates antigen initiated cell-mediated injury in the pathogenesis of AIN. Drugs account for 70% of all cases, with over 150 different agents incriminated. The remaining cases are due to infections, autoimmune diseases, and rarely idiopathic. Early tribulations and classifications notwithstanding, most diseases of the kidney continued to be considered as tubulopathies rather than glomerulopathies through the first decades of the 20th century. It is within this context that the

pathologic diagnosis of “acute interstitial nephritis” (AIN) was described in 1898 by William Thomas Councilman (1854-1933), then pathologist in chief at the BrighamHospital.

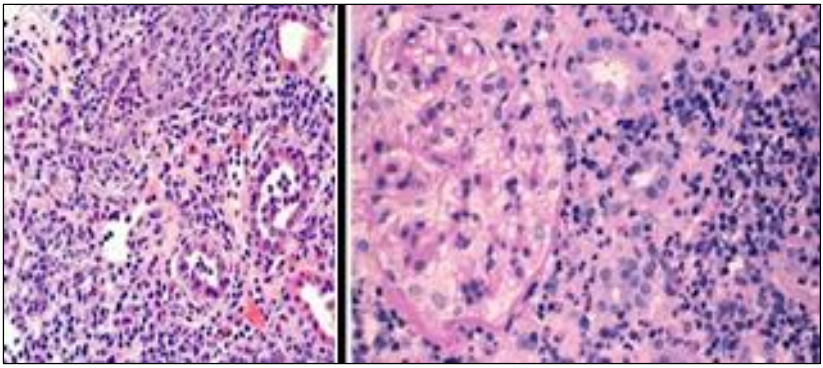


Fig 7: Interstitial Nephritis

Causes

Drugs: Penicillins, NSAIDs, allopurinol, furosemide.

Infections: Leptospirosis, tuberculosis, pyelonephritis, cytomegalovirus, Hantavirus.

Systemic disease: Sarcoidosis, Sjogren’s syndrome, myeloma. Renal biopsies show intense inflammation with polymorphonuclear leucocytes and lymphocytes surrounding tubules and blood vessels and occasional eosinophils (figure 7).

Investigations

Laboratory markers of tubular dysfunction are evident before decrements in filtration rate and consequent increments in blood urea nitrogen (BUN) and serum creatinine levels. The principal hallmarks of glomerular disease (salt retention, oedema, hypertension) are characteristically absent. The early diagnosis of acute interstitial nephritis by detecting tubular dysfunction is central to its diagnosis at a potentially reversible stage.

Chronic Interstitial Nephritis

It is defined as a “chronic inflammation within the tubule interstitium”.

Causes: chronic glomerular disease, immune/inflammatory disease, tumors (myeloma), drugs (NSAIDs, analgesic nephropathy).

Metabolic/congenital (Wilson's disease, hypokalemia, medullary sponge kidney hypercalciuria, sickle cell nephropathy), toxins (lead, Chinese herbs, Balkan nephropathy).

Clinical Features

Hypotension, polyuria, sodium and water depletion. Patients present in adult life with chronic renal failure, hypertension and small kidneys.

Polycystic Kidney Disease

Polycystic kidney disease (PKD) is an inherited disorder characterized by cystic expansion of the kidneys producing progressive kidney enlargement and renal insufficiency, in addition to various extrarenal manifestations. The disease can be inherited in autosomal dominant and recessive forms. Autosomal dominant polycystic kidney disease (ADPKD) is characterized by slow but progressive enlargement of the kidneys with renal failure occurring by the fifth to sixth decade of life. Polycystic kidney disease (PKD) is the most common genetic cause of kidney failure in adults and children. PKD is characterized by progressive cystic dilation of the renal tubules, which results in nephromegaly and often culminates in end stage renal disease. The disease occurs in approximately 1:800 to 1:1,000 people and accounts for 2.5% of all cases of end stage renal disease. In patients with polycystic kidney diseases (PKDs), the kidneys contain multiple fluid filled cysts, although other organs may also beaffected.

Pathology

Small cysts of proximal tubular epithelium are present in infancy and enlarge at a variable rate. In full developed adult polycystic kidney disease the kidneys are asymmetrically enlarged and contain numerous cysts. These differ in size and are surrounded by a variable amount of parenchyma which often shows extensive fibrosis and arteriolosclerosis.

Clinical Features

Hypertension, which may or may not be associated with deterioration of renal function. Vague discomfort in loin or abdomen due to increasing mass of renal tissue, acute loin pain or renal colic due to haemorrhage in to a cyst, haematuria, urinary tract infection, renalfailure.

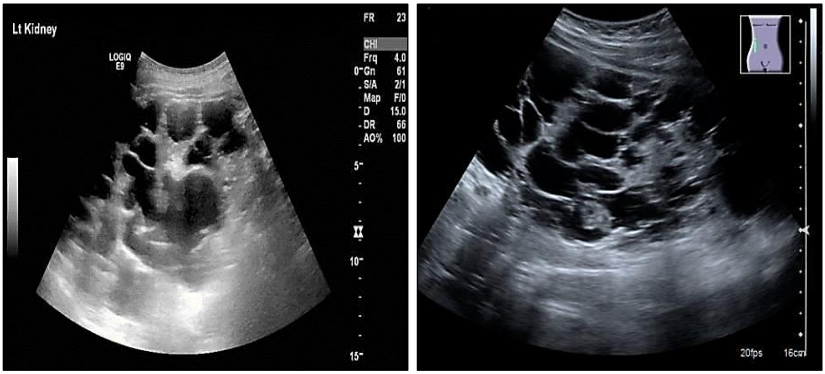


Fig 8: Polycystic kidney disease ultrasonography

Investigations

The diagnosis is made on the basis of clinical features, family history and ultrasound (figure 8).

Chapter - 5

Diseases of the Neurology

Alzheimer's disease

Alzheimer's disease exists along a spectrum, from early memory changes to functional dependence and death. Using a case illustration, we review the evaluation and diagnosis of mild cognitive impairment and the diagnosis and management of Alzheimer's disease at each stage, including the management of both cognitive and behavioral/psychiatric aspects of the disease and end-stage and end-of-life care. Dementia is a clinical syndrome characterized by progressive decline in two or more cognitive domains, including memory, language, executive and visuospatial function, personality, and behavior, which causes loss of abilities to perform instrumental and/or basic activities of daily living. Alzheimer's disease (AD) is by far the most common cause of dementia and accounts for up to 80% of all dementia diagnoses. Although the overall death ratein the United States from stroke and cardiovascular disease is decreasing, the proportion of deaths related to AD is going up, increasing by 89% between 2000 and 2014. Current treatments available include cholinesterase inhibitors for patients with any stage of AD dementia and memantine for people with moderate-to-severe AD dementia. These medications have been shown to enhance the quality of life for both patient and caregiver when prescribed at the appropriate time during the course of illness; however, they do not change the course of illness or the rate ofdecline.

Clinical Features

Both short term and long term memory are affected, apraxia, visuo spatial impairment, anosognosia, depression, cannot identify person and the clinical features are made acutely worse by coexistent intercurrent illness[2].

Management

There is no specific treatment for this condition.

Parkinson's disease

Parkinson's disease (PD) was first described by Dr. James Parkinson in 1817 as a "shaking palsy." It is a chronic, progressive neurodegenerative

disease characterized by both motor and non-motor features. The disease has a significant clinical impact on patients, families, and caregivers through its progressive degenerative effects on mobility and muscle control. The motor symptoms of Parkinson's disease are attributed to the loss of striatal dopaminergic neurons, although the presence of non-motor symptoms supports neuronal loss in non-dopaminergic areas as well. The term *Parkinsonism*is a symptom complex used to describe the motor features of Parkinson's disease, which include resting tremor, bradykinesia, and muscular rigidity. Parkinson's disease is the most common cause of Parkinsonism, although a number of secondary causes also exist, including diseases that mimic Parkinson's disease and drug- induced causes. Parkinson's disease is one of the most common neurodegenerative disorders. The Parkinson's disease Foundation reports that approximately 1 million Americans currently have the disease. Although it is primarily a disease of the elderly, individuals have developed Parkinson's disease in their 30s and 40s. Gender differences pertaining to the incidence of Parkinson's disease are reflected in a 3:2 ratio of males to females, with a delayed onset in females attributed to the neuroprotective effects of estrogen on the nigrostriatal dopaminergic system. Parkinson's disease variable but pronounced progression has a significant impact on patients, families, and society. Advanced and end- stage disease may lead to serious complications, including pneumonia, which are often associated with death.

Parkinson's disease is a disorder of the extrapyramidal system, which includes motor structures of the basal ganglia, and is characterized by the loss of dopaminergic function and consequent diminished motor function, leading to clinical features of the disease. Progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which project to the striatum (the nigrostriatal pathway), results in the loss of dopaminergic function in individuals with PD.

Typically, patients experience the motor features of Parkinson's disease only after 50% to 80% of dopaminergic neurons have been lost, suggesting the involvement of a compensatory mechanism in the early stages of thedisease.

Two types of dopamine receptors, D_1 (excitatory type) and D_2 (inhibitory type), influence motor activity in the extrapyramidal system. Components of this system include the basal ganglia, which involves the internal globus pallidal segment (GPi) of the ventral striatum, and the pars reticulata portion of the substantia nigra (SNpr). These components are part of larger circuits located in the thalamus and the cortex. The loss of

dopamine in the striatum of Parkinson's disease patients results in increased activity in the GPi/SNpr circuits and subsequent gamma aminobutyric acid (GABA) dysfunction, leading to inhibition of the thalamus. The end result is the decreased ability of the thalamus to activate the frontal cortex, resulting in the decreased motor activity characteristic of Parkinson's disease. Accordingly, restoring dopamine activity in the striatum through D_2 and D_1 receptor activation with dopaminergic therapies mediates clinical improvement in the motor symptoms of Parkinson's disease[4]. In addition, dopaminergic loss results not only in reduced activation of the thalamus but also in increased cholinergic activity due to the loss of dopamine's normal inhibitory influence.

Clinical Features

Clinical features of Parkinson's disease are tremor, rigidity, bradykinesia, may be absent initially, when nonspecific symptoms of tiredness, aching limbs, mental slowness, small handwriting may be noticed. Most patients have difficulty with rapid fine movements, tremor also affects the legs, mouth as well as tongue, slowness of gait difficulty with tasks such as fastening buttons, shaving or writing, postural righting reflexes are impaired early on in the disease, speech become softer, indistinct.

Fig 1: Parkinson's MRI brain & SPECT

Investigations

The differential diagnosis of PD should include a comprehensive history and physical examination. Difficult or questionable cases should be referred to a movement-disorder specialist for further evaluation. There are no definitive tests to confirm the diagnosis of PD; therefore, a clinical diagnosis requires the clinician to review the patient's history, to assess symptoms, and to rule out alternative diagnoses, such as multiple-system atrophy, DLB disease, and essential tremor. The cardinal motor features of PD-described as the "classical triad"-include a 4-Hz to 6-Hz resting tremor, "cogwheel" rigidity, and bradykinesia.

Management

The primary goal in the management of PD is to treat the symptomatic motor and non-motor features of the disorder, with the objective of improving the patient's overall quality of life. Appropriate management requires an initial evaluation and diagnosis by a multidisciplinary team consisting of neurologists, primary care practitioners, nurses, physical therapists, social workers, and pharmacists. Effective management should include a combination of non-pharmacological and pharmacological strategies to maximize clinical outcomes. To date, therapies that slow the progression of PD or provide a neuroprotective effect have not been identified.

Guillain Barre's Syndrome

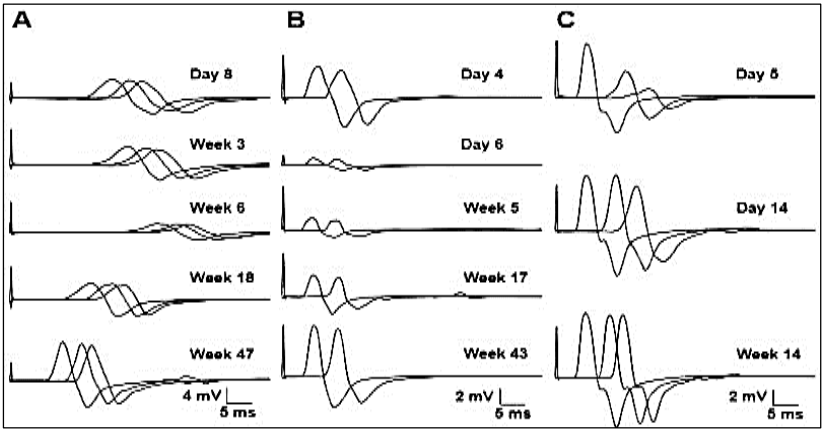
It is acute inflammatory demyelinating polyneuropathy. Guillain Barré syndrome (GBS) was first described in 1916 (Guillain G, 1916) and is approaching its 100th anniversary. Our knowledge of the syndrome has hugely expanded since that time.

Once originally considered to be only demyelinating in pathology us now recognizes both axonal and demyelinating subtypes. Numerous triggering or antecedent events including infections are recognized and GBS is considered an immunological response to these. GBS is now considered to be a clinical syndrome of an acute inflammatory neuropathy encompassing a number of subtypes with evidence of different immunological mechanisms. Some of these are clearly understood while others remain to be fully elucidated. Complement fixing antibodiesagainst peripheral nerve gangliosides alone and in combination are increasingly recognised as an important mechanism of nerve damage. New antibodies against other nerve antigens such as neurofascin have been recently described. Research databases have been set up to look at factors associated with prognosis and the influence of intravenous immunoglobulin (IvIg) pharmacokinetics in therapy. Exciting new studies are in progress to examine a possible role for complement inhibition in the treatment of thesyndrome.

Early studies reported oedema of the peripheral nerves with sparse inflammatory infiltrate. Classic studies by Asbury and colleagues emphasised the importance of perivascular lymphocytes which resembled the findings in the animal model experimental allergic neuritis.

Clinical Features

Clinical features of Guillain barre's syndromes are muscle weakness, paresthesia especially distal and limb pains often precede the weakness, facial or bulbar weakness, respiratory failure can develop within hours.



Diagnosis

A lumbar puncture should be done before treatment. A cerebrospinal fluid (CSF) white cell count of over 10/µl raises the possibility of leptomeningeal malignancy, HIV or an alternative infectious diagnosis (eg Lyme disease or poliomyelitis), but in clinical trials CSF cell counts up to 50/µl are permitted. IvIg can very occasionally cause aseptic meningitis. Typically, the CSF protein is raised after the first week, often to more than 1 g/l. Routine blood tests should include creatine kinase, biochemistry and Ig levels. These are done to exclude other causes of weakness and to reduce the risks of ivIg. In renal failure ivIg is relatively contraindicated and it is more likely to cause anaphylaxis in patients with IgA deficiency.

Management

Treatment should be started as soon as possible, but there is no evidence that starting it 12 hours earlier (e.g. overnight) makes any difference. First-line treatment is now usually ivIg because of its ease of administration. Adequate pain relief and a multidisciplinary approach to rehabilitation are essential, as is patient education during the slow but steady recovery, with improvements to be expected for up to two years.

Myasthenia Gravis

It is characterized by progressive inability to sustain a maintained or repeated contraction of striated muscle (fatigability). Acquired myasthenia gravis is a relatively uncommon disorder, with prevalence rates that have increased to about 20 per 100,000 in the US population. This autoimmune disease is characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest. In about two-thirds of the patients, the

involvement of extrinsic ocular muscle presents as the initialsymptom, usually progressing to involve other bulbar muscles and limb musculature, resulting in generalized myasthenia gravis. Although the cause of the disorder is unknown, the role of circulating antibodies directed against the nicotinic acetylcholine receptor in its pathogenesis is wellestablished.

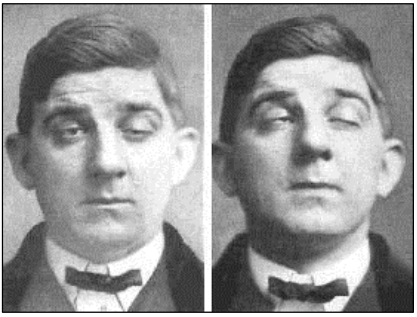


Fig 3: Myasthenia gravis

The nerve terminals innervating the neuromuscular junctions (NMJ) of skeletal muscles arise from the terminal arborization of α-motor neurons of the ventral horns of the spinal cord and brain stem. The NMJ itself consists of synaptic cleft and 20nm thick space that contains acetylcholinesterase (AChE) along with other supporting proteins/proteoglycans [12]. The NMJ postsynaptic membrane has deep folds with acetylcholine receptors (AChR) tightly packed on the top of these folds. When the nerve action potential reaches the synaptic bouton, depolarization opens voltage gated Calcium channels on the presynaptic membrane, triggering release of ACh into the synaptic cleft. The ACh diffuses into the synaptic cleft to reach postsynaptic membrane receptors where it triggers off the end-plate potential (EPP) and gets hydrolyzed by AChE within the synaptic cleft. MuSK (muscle specific tyrosine kinase), a postsynaptic transmembrane protein, forms part of the receptor for agrin, a protein present on synaptic basal lamina. Agrin/MuSK interaction triggers and maintains rapsyn-dependent clustering of AChR and other postsynaptic protein. Rapsyn, a peripheral membrane protein on the postsynaptic membrane, is necessary for the clustering of AChR. Mice lacking agrin or MuSK fail to form NMJs and die at birth due to profound muscle weakness.

Clinical Features

The disease usually presents between the age of 15 and 50 years with women affected more often than men. Symptoms are abnormal fatigable weakness of the muscles, movement is initially strong, it rapidly weakness,

ptosis, diplopia, limb muscle may be affected, mostly commonly those of the shoulder girdle, respiratory muscles may be involved, aspiration may occur if the cough is ineffectual. Sudden weakness from a cholinergic or myasthenic crisis may require ventilator support.

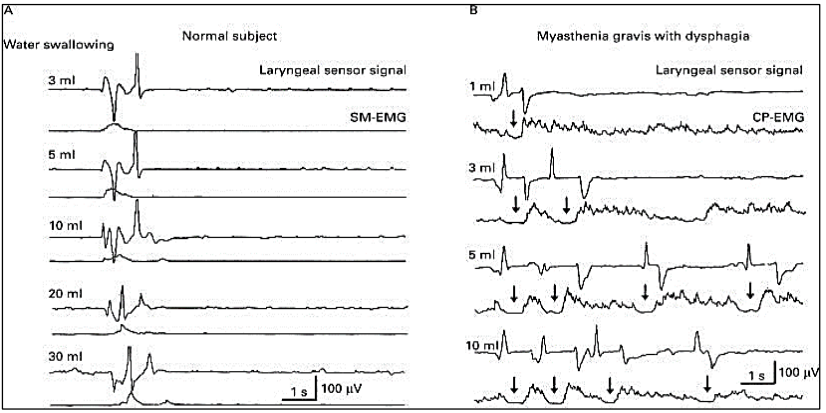


Fig 4: Myasthenia gravis electromyography

Diagnosis

For a patient with ptosis, a small cube of ice is placed over the eyelid for about 2 minutes. Improvement of the ptosis after this procedure suggests a disorder of neuromuscular transmission. All patients with MG should have a computed tomography (CT) scan of the chest done with contrast. Routine chest radiography may be done but should not be done in place of the CT scan of thechest.

Management

Thymectomy should be performed as soon as feasible in any patient with myasthenia not confined to extra ocular muscles, unless the disease has been established for more than 7 years. Plasma exchange are removing antibody from the blood may produce marked improvement.

Chapter - 6

Diseases of the Respiratory System

Chronic Obstruction Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is the name for a group of lung conditions that cause breathing difficulties. It includes:

- Emphysema-damage to the air sacs in thelungs
- Chronic bronchitis-long term inflammation of theairways

Chronic obstructive pulmonary disease is a common condition that mainly affects middle aged or older adults who smoke. Many people do not realise they have it. The breathing problems tend to get gradually worse over time and can limit your normal activities, although treatment canhelp keep the condition undercontrol.

Definition

Chronic obstructive pulmonary disease is the respiratory disorder characterized by airflow obstruction mainly resulting from chronic bronchitis, emphysema. This does not change markedly over several months. The impairment of lung function is largely fixed but may be partially reversible by bronchodilator therapy. Historically, the term chronic bronchitis was used to define any patient who coughed up sputum on most days of at least three consecutive months or more for more than two successive years. Emphysema referred to the pathological process of a permanent destructive enlargement of the airspaces distal to the terminal bronchioles. According to WHO the death rate from Chronic obstructive pulmonary disease currently exceeds 5000 per year in north, west, east, south India and this condition accounts for over 10% of all hospital medical admission in the India.

Causes

Chronic obstructive pulmonary disease is cigarette smoking and a direct correlation exists between the number of cigarettes smoked in pack year (one pack year =20 cigarettes smoked daily for one year) and the likelihood of developing the disease. Smoking is thought to have its effect by inducing

persisting airway inflammation and causing a direct imbalance in antioxidant capacity and antiproteinase/proteinase load in the lungs.

Individual susceptibility (homoeopathy) to smoking is, however, very wide, with only 15 to 20% of smokers likely to develop clinically significant Chronic obstructive pulmonary disease. A small additional contribution to the severity of chronic obstructive pulmonary disease has been reported in patients exposed to dusty or air polluted environments. Also causes of low birth weight, bronchial hyper responsiveness and the formation of chronic obstructive pulmonary disease. Alpha antitrypsin deficiency can cause emphysema in non-smokers but this risk is increased strongly in enzyme deficient patient who smoke. Stopping smoking slows the average rate of decline in forced expiration volume from 50-70 ml/year to 30 ml/year (equal to non-smokers).

Pathology

Chronic obstructive pulmonary disease patients develop airway wall inflammation hyper trophy of the mucus secreting glands and increase in the number of goblet cells in the bronchi and bronchioles with a consequent decrease in ciliated cells. Its leads to less efficient transport of the increased mucus in the airways and loss of alveolar attachments around such airway makes them more liable to collapse during expiration. Emphysema is usually centriacinar, involving respiratory bronchioles, alveolar ducts and centrally located alveoli. Paraseptal emphysema develops with the latter responsible for blebs on the lung surface and giant bullae. Pulmonary vascular remodelling caused by persistent hypoxaemia results in pulmonary hypertension and right ventricular hypertrophy and dilation.

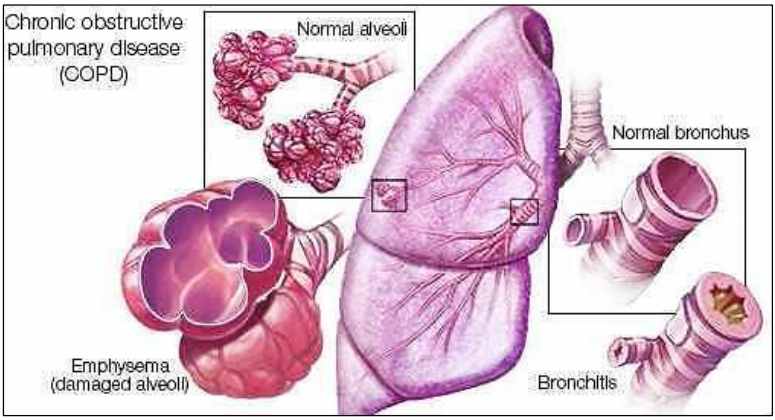


Fig 1: Difference between normal and COPD bronchus, alveoli

Clinical Features

Patient have a shortness of breath (SOB) and coughing as a normal part of aging, but these could be signs of chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease can progress for years without noticeable shortness of breath. Symptoms of chronic obstructive pulmonary disease can be different for each person, but common symptoms are:

- Increased shortness of breath
- Frequent coughing (with and without mucus)
- Increased breathlessness
- Wheezing
- Tightness in the chest

Patients will suffer recurrent respiratory infections, exertional breathlessness, regular morning cough, severe wheeze. Sputum may be scanty, mucoid, tenacious and occasionally streaked with blood during infective exacerbations. Frankly purulent sputum is indicative of bacterial infection. Shortness of breath is aggravated by infection, excessive cigarette smoking and adverse atmospheric condition. In auscultation method can find crepitations (crackles) which usually, but not always, disappear after coughing may be clear audible over lower zones.

Classification of Chronic obstructive pulmonary disease: It is divided in to mild, moderate and severe. In mild Chronic obstructive pulmonary disease is spirometry Forced expiration volume is 60-70% predicted and symptoms are smokers cough or exertional breathlessness.

In moderate Chronic obstructive pulmonary disease is Forced expiration volume is 40-50% predicted and exertional breathlessness, cough, sputum and wheeze presented. In severe Forced expiration volume is 60-70% predicted is Forced expiration volume is less than 40% predictedand exertional breathlessness, cough, sputum, wheeze and swollen legs presented.

Investigation

Investigation of chronic obstructive pulmonary disease is spirometry, pulse x ray of chest (anterior posterior view and lateral view), pulse oximetry to know the oxygen percentage and haematology (polycythemia may develop but should not be assumed to be secondary without measurement of P_aO_2).

CT scan can be used to quantify the extent and distribution of emphysema.

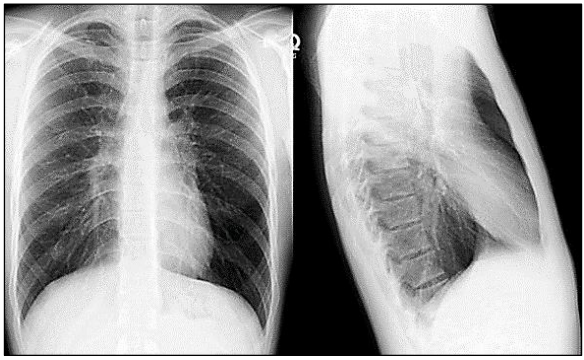


Fig 2: Chest radiograph of chronic obstructive pulmonary disease

Management

Chronic obstructive pulmonary disease can be managed by antibiotics, stop smoking completely/permanently, bronchodilator therapy, surgical intervention, homoeopathic medication.

Bronchiectasis

It is defined as a 'abnormal dilation and chronic enlargement of the bronchi/bronchus'. The passageways from the trachea to the alveoli that are the air exchanging parts of the lungs. It may be acquired or less commonly, congenital. Bronchiectasis may occur in a single portion of the lung (localized) or throughout the lungs (diffuse) and is the major lung abnormality of cystic fibrosis. It may have several different contributing factors, such as abnormal cilia, and its course may vary greatly from causing no symptoms to causing death.

Etiology of Bronchiectasis

- Congenital cause of bronchiectasis is ciliary dysfunction syndromes like primary ciliary dyskinesia (immotile cilia syndrome), kartagener's syndrome, young syndrome, cystic fibrosis and primary hypogammaglobulinemia
- Acquired in children causes are pneumonia (complication, whooping cough or measles), primary tuberculosis, foreignbody
- Acquired in adults causes are suppurative pneumonia, pulmonary tuberculosis, allergic bronchopulmonaryaspergillosis and bronchial tumors

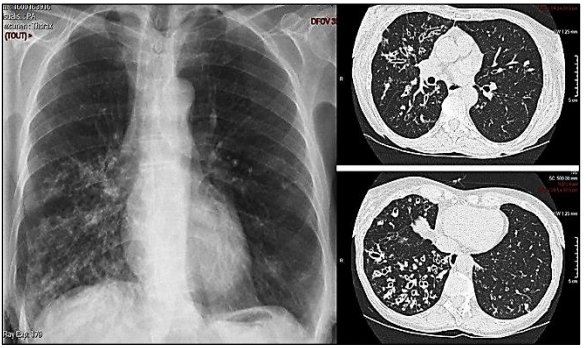


Fig 3: Chest Radiograph and CT images of Bronchiectasis

Pathology

Bronchiectasis cavities may be lined by granulation tissue, squamous epithelium or normal ciliated epithelium. There may also be inflammatory changes in the deeper layers of the bronchial wall and hypertrophy of the bronchial arteries. Chronic inflammatory and fibrotic changes are usually found in the surrounding lung tissue.

Clinical Features

Bronchiectasis may occur any part of the lungs, but the more efficient drainage by gravity of the upper lobes usually produces less serious symptoms and complication than the lower lobes. Chronic productive of cough usually aggravated by morning and often brought on by changes of posture. Sputum often copious and persistently purulent in advanced disease (due to accumulation of pus in dilated bronchi/bronchus). Fever, malaise and increased cough, sputum volume when spread of infection causes pneumonia, which is frequently associated with pleurisy. Recurrent pleurisy in the same site often occurs in this condition (due to inflammatory changes in lung and pleura surrounding dilated bronchi). Purulent sputum, haemoptysis. It is called dry bronchiectasis.

Associated symptoms are weight loss, anorexia, lassitude, excessive sweating at night time and digital clubbing.

Investigation

In advanced disease the cystic bronchiectasis spaces may be visible. Abnormalities produced by associated pulmonary infection and collapse are evident. A diagnosis of bronchiectasis can only be made with certainty by CT scan. Ciliary function test when patients suspected of having a ciliary dysfunction syndrome.

Management

Bronchiectasis can be managed with postural drainage, antibiotic therapy, surgical treatment and homoeopathic treatment.

Cystic Fibrosis

Cystic fibrosis (CF) is the most common, life shortening genetic disease in Caucasians. It affects the transport of salt and water across cells and affects different organs, but lung disease is responsible for the majority of symptoms, burden of care, and lost years of life. The gene that causes the disease has now been identified andsequenced.

Epidemiology

Cystic fibrosis affects at least 30,000 people in the United States; between 900 and 1,000 new cases are diagnosed every year (1). One in 29 people of Caucasian ancestry is an unaffected carrier of the CF gene mutation. In the United States, cystic fibrosis occurs at a rate of 1 in 3,400 births. While it occurs in persons of all racial and ethnic backgrounds, it is most common in Caucasians of Northern European ancestry. Historically, half of affected individuals were diagnosed by five months of age, though the average age at diagnosis was five years, and some individuals were not diagnosed until adulthood. In 2010, however, all states began requiring that newborns undergo screening for cystic fibrosis. This should be helpful because early diagnosis and treatment reduce symptoms, improve health, and reduce costs associated with diseasecomplications.

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene.

A recessive genetic disorder, it is inherited when two carrier parents (who have one normal gene and one gene with a mutation) each contributes the abnormal CFTR gene to their child. Thus, the likelihood that two carrier parents will have an affected child is 1:4 for each pregnancy.

The abnormality in the CFTR gene causes a defective CFTR protein to be produced, resulting in abnormal transport of salt (sodium and chloride) and water across cells that line the respiratory, digestive, and genital tracts. This results in a reduction of water in the fluid lining the airways. Diminished water causes the respiratory secretions to become thicker and clog small airways. The stagnant sputum becomes infected as bacteria that are inhaled or brought into the lungs through the mouth become lodged there. Persistent stagnation allows persistent infection and chronic inflammation to develop. Inflammatory cells trapped in the sputum add to itstenacity.

Clinical Features

The bronchi dilate and their walls weaken, setting up a condition called bronchiectasis that results in further airflow obstruction. The vicious cycle of airway obstruction, inflammation, and persistent infection leads to a progressive decline in lung function and eventually causes respiratory failure and death.

Clogged mucus secretions in the digestive tract can lead to malnutrition and vitamin deficiencies. The genital tract abnormality can lead to infertility in men and women.

Environmental exposures worsen cystic fibrosis lung disease. Children who are exposed to tobacco smoke have lower lung function and more pulmonary exacerbations than those who live in smoke free environments. High levels of air pollution are associated with an increased rate of adverse pulmonaryevents.

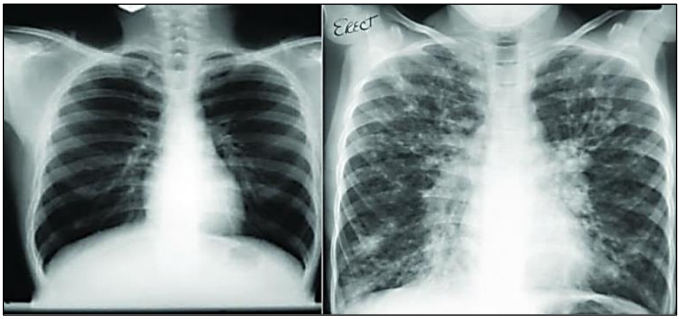


Fig 4: Chest radiograph of cystic fibrosis

Management

All the patients with cystic fibrosis who produce sputum should have regular chest physiotherapy, which should be performed more frequently during exacerbations. Cystic fibrosis can be managed by potential for somatic gene therapy and homoeopathic constitutional remedies.

Pneumonia

Pneumonia is a “lung infection characterized by severe cough and fever mainly resulting from bacteria, virus or fungi”. It involving the lung alveoli (air sacs) and can be caused by microbes, including bacteria, viruses, or fungi. It is the leading infectious cause of hospitalization and death in the India and exacts an enormous cost in economic and human terms. Healthy individuals can develop pneumonia, but susceptibility is greatly increased by a variety of personal characteristics. Community acquired pneumonia occurs

outside of the hospital (Streptococcus pneumonia), hospital acquired pneumonia occurs contracted by a patient in a hospital at least 48-72 hours after being admitted. It is bacterial infection rather than viral infection. It includes post-operative pneumonia and most common pathogens are gram negative bacilli(staphylococcus).

Pneumonia was described 2,500 years ago by Hippocrates, the father of medicine. Pneumonia occurs commonly in individuals living in theirhome communities (community acquired pneumonia) as well as in individuals who are hospitalized for other reasons (hospital acquired pneumonia). The lobular Pneumonia is a radiological and pathological term refereeing to homogeneous consolidation (red hepatisation) of one or more lung lobes, often with associated pleural inflammation. Bronchopneumonia referees to more patchy alveolar consolidation associated with bronchial and bronchiolar inflammation often affecting both lowerlobes.

Stages of Pneumonia

Four stages of lobar pneumonia have been described. In the first stage, which occurs within 24 hours of infection, the lung is characterized microscopically by vascular congestion and alveolar edema. Many bacteria and few neutrophils are present. The stage of red hepatization(2-3 d), so called because of its similarity to the consistency of liver, is characterized by the presence of many erythrocytes, neutrophils, desquamated epithelial cells, and fibrin within thealveoli.

In the stage of gray hepatization (2-3 d), the lung is gray brown to yellow because of fibrinopurulent exudate, disintegration of RBCs, and hemosiderin. The final stage of resolution is characterized by resorption and restoration of the pulmonary architecture. Fibrinous inflammation may lead to resolution or to organization and pleuraladhesions.

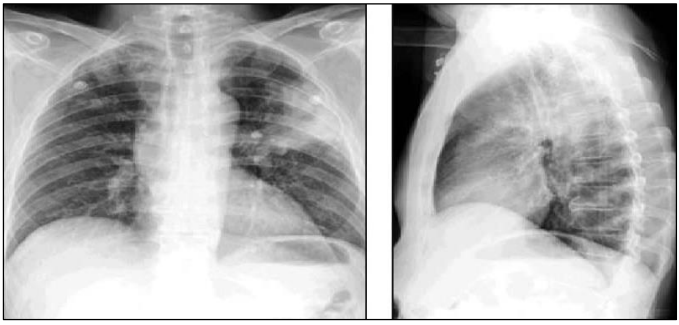


Fig 5: Radiograph of Pneumonia

Clinical Features

Patients present with complains of severe cough, high grade fever, malaise, often associated with pleuritic chest pain, which is occasionally referred to the shoulder or anterior abdominal wall. The cough is characterized by short, painful and at first dry, but later becomes productive and may become rust coloured or even frankly blood stained. The sudden onset of rigors due to high grade fever, in children vomitingor a febrile convulsion. Appetite is usually lost and headache is a frequent accompanying symptoms. In advance pneumonia confusion can be an early and dominantproblem.

Physical signs tachycardia, hypoxaemia, hypotension, confusion and tachypnoea. Pleurisy often results in diminution of respiratory movements and a pleural rub on the affected side. At a variable time after onset, generally within two days, signs of consolidation appear. The percussion note and high pitched bronchial breath sounds.

If a pleural effusion develops, physical signs of fluid in the pleural space are usually found, but bronchial breath sounds can persist and thepresence of an empyema may be suspected only from the recurrence or persistence ofpyrexia.

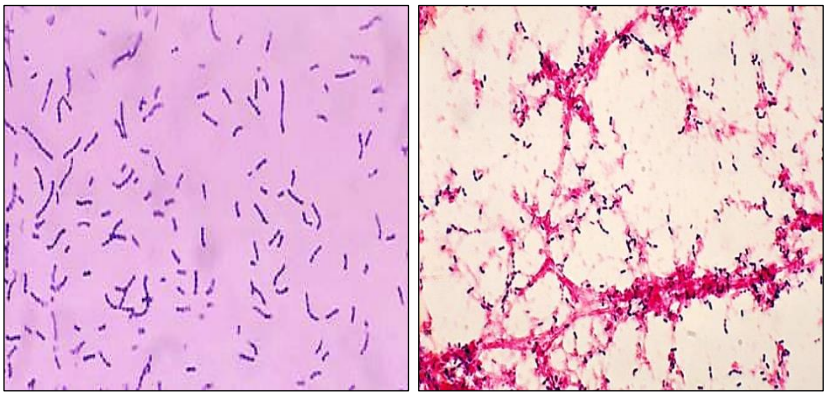


Fig 6: Gram positive diplococci characteristic of strep. Pneumonia

Investigations

In lobar pneumonia, the chest radiograph shows a homogeneous opacity localized to the affected lobe or segment; this usually appears within 12 - 18 hours of the onset of the illness. Radiological examination is also particularly helpful if a complication such as pleural effusion, intrapulmonary abscess formation or empyema is suspected.

Differential Diagnosis

- Pulmonary infraction like bacterialpneumonia
- Pulmonary/pleural tuberculosislike
- Pulmonary oedema, especially if unilateral andlocalized
- Inflammatory conditions below the diaphragm condition such as cholecystitis, peptic ulcer, acute pancreatitis, hepaticamoebiasis
- Pulmonary eosinophilia, wegener'sgranulomatosis

Management

Pneumonia can be manage by oxygen should be administered to all hypoxaemic patients, antibiotic treatment, mild analgesics for pleural pain, physiotherapy, homoeopathic medicines.

Tuberculosis

Tuberculosis remains one of the major global health threats leading to morbidity and mortality. One in three persons across the world representing 2-3 billion individuals are known to be infected with Mycobacterium Tuberculosis (M. Tuberculosis) of which 5-15% are likely to develop active. In 2014, an estimated 9.6 million people fell ill due to tuberculosis, around 1.5 million people died from the disease including 1.1 million HIV negative persons and 400,000 HIV patients. While tuberculosis is present in every country majority of tuberculosis sufferers live in low income and middle income countries especially in regions such as Sub Saharan Africa and South East Asia. Over the past decade, significant progress has been made towards tuberculosis control with most of the tuberculosis targets set as part of the Millennium Development Goals having beenachieved.

In all, effective diagnosis and treatment of tuberculosis has been estimated to have saved over 40 million lives between 2015 and 2019. The End tuberculosis strategy serves as the key guide for countries to reduce tuberculosis deaths by 90% by 2030 as well as achieve an 80% reduction in tuberculosis incidence rate compared with 2015. In this respiratory disorder paper, I provide a general overview of tuberculosis by highlighting the basics.

Pathology

The initial primary tuberculosis usually formed in the lung, but occasionally in the tonsil or alimentary tract, especially the ileocaecal region. Primary infection differs from subsequent infections in that the primary focus in lung, tonsil or bowel is almost invariably accompanied by caseous

lesions in the regional lymph nodes, such as the mediastinal, cervical or mesenteric groups respectively. Primary infection and the associated lymph node lesions heal and calcify.

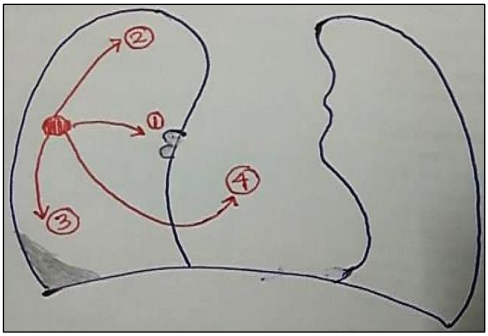


Fig 7: Primary pulmonary tuberculosis

1) Spread from primary focus to hilar and mediastinal lymph glands to form the primary complex
2) Direct extension of the primary focus-Progressive pulmonary tuberculosis
3) Spread to the pleura pleural effusion
4) Blood borne spread: Pulmonary, skeletal, renal, genitourinary; massive spread-military tuberculosis and meningitis

In a few, healing, particularly in lymph nodes, is incomplete and viable tubercle bacilli may enter the blood stream. Lesions more common in the lungs, bones, joints and kidneys and lesions may develop months or even years after primary infection. Sometimes primary infections do not heal.

Infection may also be carried by lymphatics from tuberculosis mediastinal lymph nodes to the pleura or pericardium, with the production of tuberculosis pleurisy or pericarditis. Rarely a caseous tuberculosis focus ruptures in to a vein and produces acute dissemination throughout the body, a condition known as *acute military tuberculosis*. Meningitis often complicates this condition. *Post primary pulmonary tuberculosis* characteristic pathological feature of which is the tuberculous cavity, formed when the caseated and liquefied centre of a tuberculous pulmonary lesion is discharged in to a bronchus. Blood bonrne dissemination to other organs is uncommon in post primary pulmonary tuberculosis.

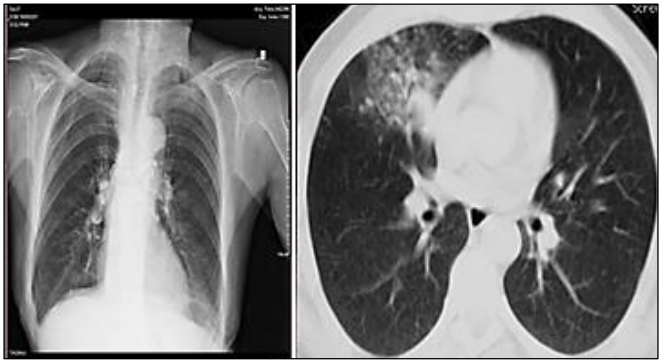


Fig 8: Radiograph & C T of Pulmonary tuberculosis

Clinical Features

Persistent cough, haemoptysis, pleural pain not associated with an acute illness, spontaneous pneumothorax, lethargy, weight loss.

Investigation

Microscopy

Sputum smear microscopy still remains the basis for diagnosis of tuberculosis in developing countries. Sputum smears can be screened using fluorochrome stains such as an auramine stain where mycobacteria appear as fluorescent rods against a dark background using an ultraviolet light microscope. Other specimens should be stained using the Ziehl-Neelsen method-mycobacteria are seen as pink rods against a blue or greenbackground.

Culture

Culture still remains the gold standard for diagnosis of tuberculosis, and it also permits the diagnosis of drug resistance, including the emerging mutations. Traditional egg based (Lowenstein Jensen) and agar based (Middlebrook 7H10/11) methods are widely used. Patients with pulmonary disease should have three sputum samples sent for microscopy and culture. If sputum is not expectorated, an induced sputum, bronchoalveolar lavage or gastric aspirate can be examined. Gastric aspirates are particularly useful in diagnosing children. Other specimens taken depend on the sites affected, but may include cerebrospinal fluid (CSF), blood, peritoneal and pericardial fluid, early morning urine, lymph node aspirates or tissue samples. CSF should be tested for cell count, protein and glucose because tuberculous meningitis is associated with an elevated lymphocyte count, high protein and lowglucose.

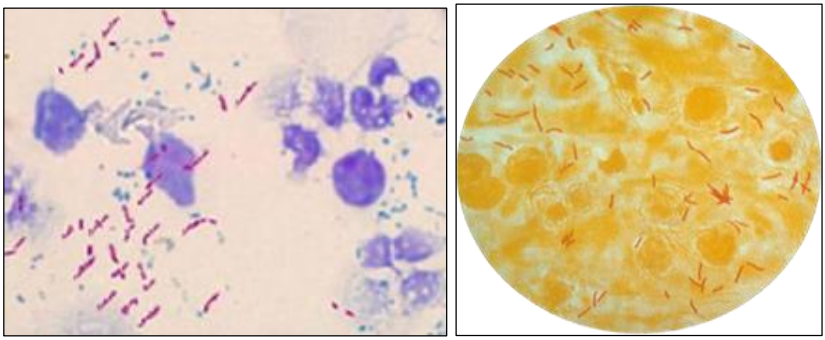


Fig 9: Examination of sputum

Tuberculin Skin Testing

Popularly known as Mantoux test involves injecting the purified protein derivative (PPD) of mycobacterial tuberculosis intradermally in the forearm and the resulting reaction is read after 48-72 hours. A positive skin test is indicated by a skin reaction at the point of the injection. A blood test has recently been developed which measures interferon g released from T cells in response to stimulation with mycobacterial antigens. Studies using ESAT-6 and CFP-10, two antigens absent from the BCG vaccine strain, have shown promising results for the diagnosis of active and latent infection.

Management

BCG is a strain of bovine tuberculin of low virulence which is used for intradermal vaccination (0.1 ml of reconstituted freeze dried vaccine), conferring protection for up to 7 years. Vaccination reduces the incidence of pulmonary tuberculosis in young adults by 80% and minimizes the risk of serious disseminated disease-military tuberculosis and tuberculous meningitis.

Chemoprophylaxis: Healed tuberculous scars may still contain viable bacteria and if cellular immunity is suppressed for any reason there may be recrudescence ofdisease.

Chemotherapy: Is the mainstay of modern treatment of tuberculosis, although the occasional patient still requires surgery for drainage of an empyema, caseating tuberculous lymph nodes or more rarely, resection of bronchiectasis areas of the lung, or emergency surgery to prevent spinal paraplegia, antituberculosis drugs (ATD) and homoeopathy medicines used in tuberculosis.

Bronchial Asthma

Bronchial asthma is heterogeneous pulmonary disorder characterized by recurrent episodes of cough, breathlessness and wheezing, which may resolve spontaneously or after the use of bronchodilator medication. The global prevalence of asthma is anticipated to be approximately 4.5 percentages. There are about 334 million patients with asthma affecting all age groups, across the world. The prevalence of asthma has increased over time and an additional 100 million people worldwide are expected to develop asthma by the year 2025.

The prevalence of asthma has increased over time and an additional 100 million people worldwide are expected to develop asthma by the year 2025. Although asthma is a major health problem in the world, there are some important issues, particularly its management. Asthma is seen in all ages of life, from earliest infancy up to old age. It has observed that males were more prone to asthma than the female.

Etiology

Heredity: It is estimated that about 30 percent of patients will give us a family history of allergy and asthma or either of these.

Allergies: Allergies can be allotted in large number of patients for causing or precipitating asthmatic assaults. Usually, a massive exposure to allergens is followed by an acute asthmatic attack. In immediate onset of asthma, the symptoms of asthma (acute occur within a few minutes of exposure.

Environmental Cause: Winds, rains, sudden changes in the climate aggravate allergic manifestations. Physical agents like colds, hearts etc., do start an allergic phenomenon and hence could be called as pseudo allergens.

Emotional: Emotional disturbances do play a vital role in the llife of an asthmatic.

Infections: Repeated upper respiratory infections are the main precipitating factors in m any cases.

Type of Asthma

Extrinsic is hereditary disposition. It starts early in life and serum levelsof IgE are elevated. It occurs due too pollens of trees, grass andweeds.

Intrinsic Asthma: it is also known as idiopathic asthma. Serum IgE levels are normal. It usually starts late in life and perennial symptoms are common.

Catarrhal asthma/millers asthma is seen in association with acute or chronic catarrhal disorders, the mucous membrane of the throat and bronchial tubes being in a n altered state, in severe cases badly inflamed.

Hay asthma is a type of asthmatic breathing that occurs in association with acute bronchial irritation and catarrh. It is summer catarrhal affection that passes under the name of rose cold or hay fever.

Miller's asthma is frequently applied to spasmodic group or laryngismus stridulus and by some authors is still mentioned as a type of asthma occurring children.

Atopic asthma is definite antigenic etiology. There is a definite history of allergy and through the hyper sensitivity tests one finds that the patient shows a positive result.

Non atopic asthma is no allergic factor in this kind of asthma. Intrinsic asthmatics when tested for IgE levels would not have a rise in IgE levels.

Pathophysiology

Current theoris include early exposure toaero allergens, early viral infections, diet or paradoxically, fever childhood infections resulting from improved public health standards.

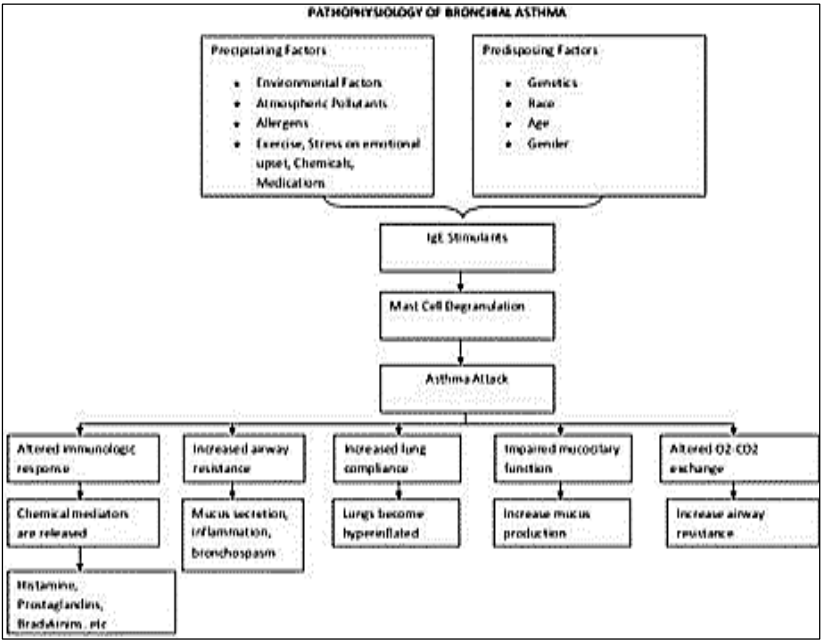


Fig 10: Pathophysiology of asthma flow chart

Clinical Features

In episodic asthma paroxysms of wheeze and dyspnoea occur at any hour of the day or night are of sudden onset and may be preceded by a feeling of tightness in the chest. Expiration is exhausting, while inspiration is short and gasping. Patient adopts to an upright position, fixing the shoulder girdle to assist the accessory muscles of expiration. In severe attacks there is tachycardia, pulsus paradoxus and central cyanosis. The symptoms usually sets in suddenly and generally at night, occurring, as a rule, without the least premonition, although it may be attendee inchildren by a stage of cold, cough and ordinary catarrhal symptom prior to the development of asthmaticbreathing.

The eyes are prominent and starring and the patient is compelled to lie or sit with his mouth partly open in order to get sufficient breath for his needs. The temperature usually not elevated, and may even be subnormal. The surface is usually cold and clammy and sometimes cyanosis is so pronounced that a fatal issue is feared.

Investigation

Completed blood picture, x- ray, sputum examination, ECG, pulmonary function test, arterial blood gases, measurement of serum IgE, detection of IgE antibody etc.,

Management

In acute severe asthma has to give oxygen, high doses of inhaled beta 2 adrenoreceptor agonists, systemic corticosteroids. In chronic asthma can be managed with homoeopathicmedicines.

Pleural Effusion

Pleural effusion is used when serous fluid accumulates in the pleural space. The passive transudation of fluid in to the pleural cavity occurs in cardiac failure and in conditions causing hypoproteinemia such as nephritic syndrome, liver failure and severe malnutrition. Pleural effusion may be unilateral or bilateral. Bilateral effusion often occurs in cardiac failure, but is also seen in much less common disorders such as the connective tissue diseases and hypoproteinemia.

Etiology

There are many causes of pleural effusions. The following is a list of some of the major causes: pneumonia, tuberculosis, pulmonary infract, malignant disease, subdiaphragmatic disorder (subphrenic abscess,

pancreatitis etc.), cardiac failure, hypoproteinemia (nephritic syndrome, liver failure, malnutrition), connective tissue disease, acute rheumatic fever, post myocardial infarction syndrome, meigs syndrome (ovarian tumour plus effusion), myxoedema, uraemia, asbestos related benign pleural effusion, yello nail syndrome.

Symptoms

Chest pain, difficulty breathing, painful breathing (pleurisy), cough is either dry or productive. Deep breathing increase pain, fever, chills, loss ofappetite.

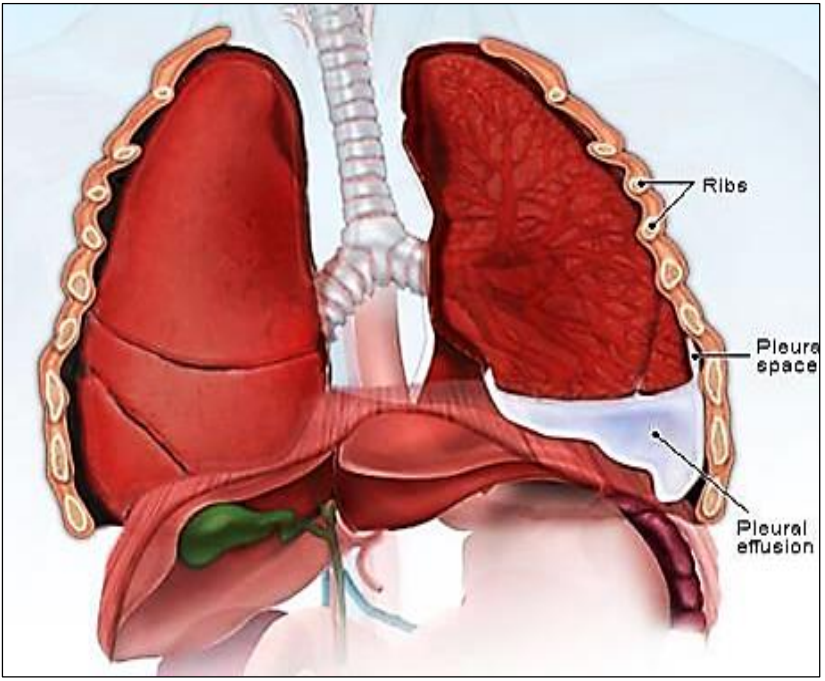


Fig 11: Pleural effusion

Investigations

Radiological examination shows a dense uniform opacity in the lower and lateral parts of the hemithorax, shading off above and medially in to translucent lung (see figure 12). Occasionally the fluid is localized below the lower lobe (subpulmonary effusion), the appearances simulating an elevated hemidiaphragm. A localized opacity may be seen when the effusion is loculated-for example in an inter lobar fissure. Ultrasonography helps to localize an effusion prior to aspiration and pleural biopsy. Pleural aspiration

can absolute proof that an effusion is present can be obtained only by the aspiration fluid. Pleural biopsy is always indicated whenever a diagnostic aspiration of pleural fluid is performed because the chances of obtaining a diagnosis from pleural biopsy material are much greater than by examination of the pleural liquid alone.

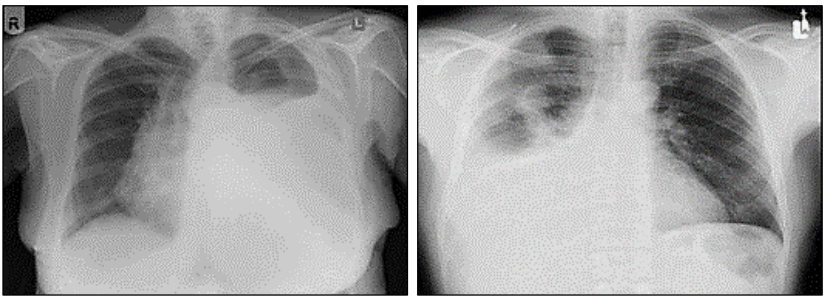


Fig 11: Radiograph of Pleural effusion

Management

Aspiration of pleural fluid may be necessary to relieve breathlessness. It is inadvisable to remove more than one liter on the first occasion because re expansion pulmonary oedema occasionally follows the aspiration of larger amounts.

Empyema

The term empyema defines “pus in the pleural space”, gram-positive, or culture from the pleural fluid. Empyema is usually associated with pneumonia but may also develop after thoracic surgery or thoracic trauma. In the United States, there are approximately 32,000 cases per year. Empyema is associated with elevated morbidity and mortality, around 20% to 30% of patients affected will either die or required further surgery in the first year after developing empyema. Early intervention is crucial in the management ofempyema.

Etiology

Around 20% of patients with pneumonia will develop a parapneumonic effusion that may lead to empyema. Seventy percent of patients with empyema have parapneumonic effusion, the other 30% of cases are related to trauma, post thoracic surgery, esophageal ruptures, or cervical infections, and a small number are not related to previous pneumonia or intervention, this is known as primary empyema. Also, comorbidities of the patients need to be taken into consideration. For community-acquired empyema, gram positive bacteria are more common, especially S*treptococcus* species. In this

setting, the presence of gram-negative bacteria has been associated with increased comorbidities of patients with alcohol abuse, gastroesophageal reflux disease (GERD), and diabetes. In hospital acquired empyema, *Staphylococcus aureus* arecommon.

Pathophysiology

Development of empyema can be described in a sequence of events. During an inflammatory process such as pneumonia, there is an increase in fluid production in the pleural cavity known as the exudates stage. As the disease progresses microorganisms, usually bacteria, can colonize the fluid and generated an empyema. This fluid is characterized by elevated lactate dehydrogenase, proteins, neutrophils, and deadcells.

Macroscopically is a thick opaque fluid found in the fibrinopurulent stage. After the resolution of the infection and as a consequence of the inflammation, there is a process of fibrosis that can lead to restriction of the lung parenchyma. Appropriate and early intervention is vital to decrease complications and mortality.

Clinical Features

The presentation may be similar to pneumonia, and cough, sputum production, fever, and pleuritic type chest pain may be present. Patients with empyema may have symptoms for a more extended period. Research has shown that patients presented after a median of 15 days after the onset of symptoms. On physical exam there may be dullness to percussion on the affected area, egophony, increase palpable fremitus, and finecrackles.

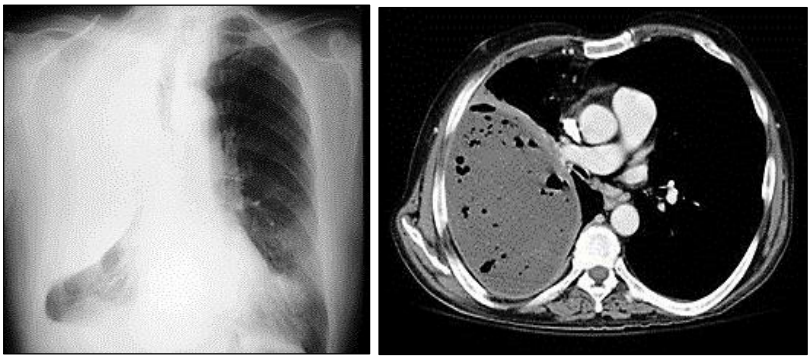


Fig 12: Radiological & CT of Empyema

Investigation

To evaluate for the presence of any pleural effusion, the first test that should be ordered is a chest x-ray. It is a widely available and simple test,

but it is not 100% sensitive. A certain amount of fluid needs to be present to be detected, usually 75 ml in a lateral view, and approximately 175 ml in an anterior view. On an x-ray, some of the characteristics of a pleural effusion are blunted due to costodiaphragmatic angles and lungs filled with radiolucent fluid. If an effusion is suspected with the chest x-ray, the next step is anultrasound.

Ultrasound is increasingly common because of its benefits, namely because it is widely available, it can be done at a patient's bedside, it is more sensitive at identifying pleural effusions than an x-ray.

It allows differentiation between parenchyma and pleural fluid, and it also has a therapeutic use. Ultrasound can be useful in guiding a chest tube placement during thoracentesis. CT scan of the chest must be done in patients with empyema. It may be an alternative option after a chest -ray or ultrasound. CT scan ideally is done with intravenous (IV) contrast to enhance the pleura. CT scan can also be diagnostic and therapeutic, thoracentesis and tube thoracotomy can be performed under this modality. Some of the characteristics on CT scan are thickening of the pleura (present in approximately 80% to 100% patients), pleural enhancement, split pleural sign, bubbles in the absence of tube drainage, and septation. With a CT scan practitioners can better assess the lung parenchyma and the position of a chesttube.

Management

Treatment of empyema usually involves medical and surgical treatment. In community-acquired empyema, use antibiotics. Antibiotic should be given for 2 to 6 weeks, depending on patient response, source control, and organism. Tube thoracostomy is the most common type of drainage, bore tube versus smaller tubes have not shown any difference regarding mortality and prognosis, but bigger tubes are associated with more pain. For this reason, small tubes are frequently placed. The position of the tube should be confirming with an x-ray or CT scan. Lack of clinical improvement in the first 24 hours is usually related to tube malposition or blockage. Blockage of the chest tube can be prevented with frequent flushing, but the necessary amount and frequency of this process is unclear. Any indication of a persistent fluid or other locations should be addressed with more aggressive therapy including a larger tube, more tubes, or surgery. The chest tube can usually be removed when the daily production of pleural fluid is proximal 350 ml/day orless.

Chapter - 7

Diseases of the Hepatic System

Jaundice

Jaundice/Hyperbilirubinemia define as “the yellow discoloration appearance of the sclera, skin and mucous membranes resulting from an increased bilirubin concentration in the body fluids”. It is a multifactorial disorder with many symptoms. Generally, the physiological jaundice is the most prevalent type however in some regions pathological jaundice is also common. This review article focuses on a brief introduction to jaundice, its types and causes, measuring the bilirubin level, clinical approaches towards hyperbilirubinemia, different precautionary measures for the parents of babies suffering from hyperbilirubinemia. Acute jaundice is often an indicator of significant underlying disease and occurs secondary to intra and extra hepatic etiologies. A retrospective study of more than 700 individuals found that most cases (55%) of acute jaundice in adults are caused by intra hepatic disorders, including viral hepatitis, alcoholic liver disease, and drug induced liverinjury.

The remaining 45% of acute jaundice cases are extra hepatic and include gallstone disease, hemolysis, and malignancy. My article provides a systematic approach to the diagnosis of jaundice in adults and reviews common etiologies of hyperbilirubinemia. It is detectable clinically when the plasma bilirubin exceeds 3 mg/dl. Internal tissues and body fluids are coloured yellow but not the brain.

Unconjugated bilirubin is produced (250-300mg daily) from the catabolism of haem after removal of its iron component. Unconjugated bilirubin is conjugated by the endoplasmic reticulum enzyme. Glucuronyl transfers, in to bilirubin mono and diglucuronide.

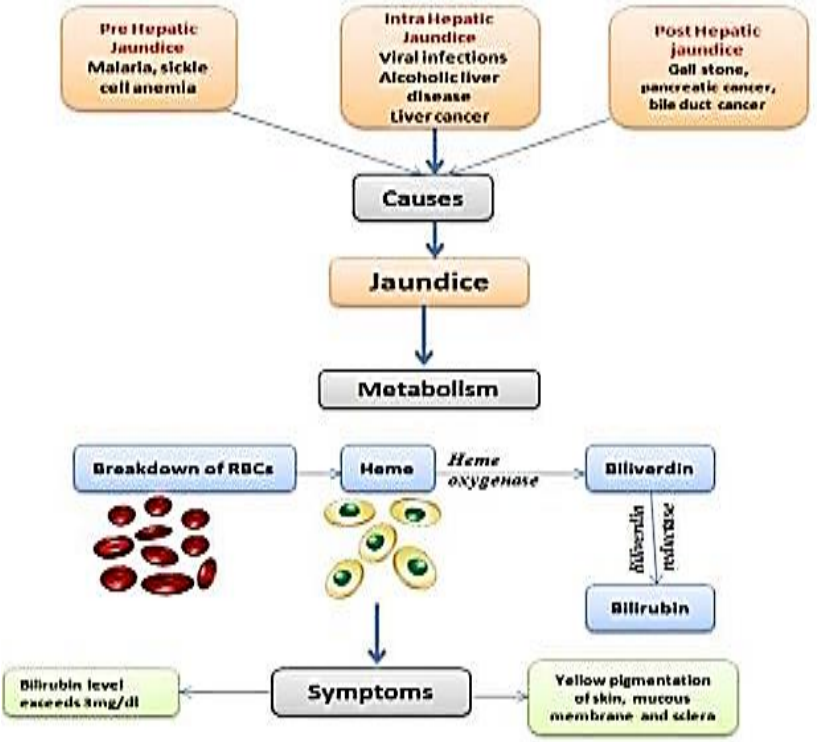


Fig 1: Pathophysiology of jaundice

Causes

Causes of cholestatic jaundice is Primary biliary cirrhosis, primary sclerosing cholangitis, alcohol, drugs, viral hepatitis, autoimmune hepatitis, severe bacterial infections, post-operative, hodgkin's lymphoma, pregnancy, idiopathic recurrent cholestasis and extrahepatic is carcinoma of ampullary pancreatic, bile dut, cystic fibrosis, parasitic infection and traumatic biliary structures.

Clinical features

In cholestasis early symptoms are dark urine, pale stools, pruritus. Cholangitis are fever, rigors, pain and hepatic abscess. Late features are xanthelasma and xanthomata, malabsorption are weight loss, steatorrhoea, osteomalacia and bleeding tendency.

Investigations

In portal/hepatic venous obstruction can do angiography. Ultrasound in cases of dilated bile duts and abnormal parenchyma/no dilated ducts. PTC,

ERCP in case of dilated bile ducts and liver biopsy for abnormal parenchyma. Focal liver lesions (tumor, cyst, abscess) are fine needle aspiration/FNA.

Ascites

It is free fluid in the peritoneal cavity.

Causes

Common causes of ascites are malignant disease (hepatic, peritoneal), cardiac failure, hepatic cirrhosis and other causes are hypoproteinemia-nephritic syndrome, protein-losing enteropathy, malnutrition.

Hepatic venous occlusion like budd chiari syndrome, veno occlusive disease, infection-tuberculosis, spontaneous bacterial, peritonitis, pancreatitis, lymphatic obstruction, rare-meigs syndrome, vasculitis, hypothyroidism, renal dialysis.

Pathogenesis

Liver failure and portal hypertension in cirrhosis cause sodium and water retention in the body. Because of this cause localization of fluid collection in the peritoneum due to the high venous pressure in the mesenteric circulation. The means where by Na+ and water retention occurs are unknown.

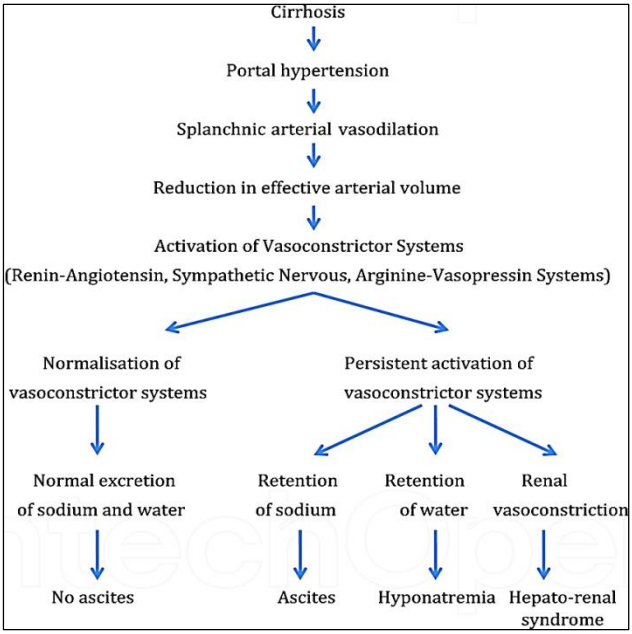


Fig 2: Pathophysiology of Ascites

The mechanisms for renal sodium retention remain poorly understood but include activation of the rennin angiotensin system with secondary aldosteronism, increased sympathetic nervous activity, alteration of atrial natriuretic hormone secretion and altered activity of the kallikreinkinin system.

Clinical Features

It causes abdominal distension with fullness in the flanks, shifting dullness on percussion, divarication of the umbilicus, hernia, abdominal striae, meralgia paresthetica, scrotal oedema. Pleural effusion can be found in some cases, usually on the right side.

Investigation

Ultrasonography can confirm ascites. Abdominal radiographs can show ascites, but they are insensitive and non-specific. Ascites protein concentrations below 25 g/l or serum ascites albumin gradients above 1.5 are usually found in ascites due to cirrhosis. Cytological examination can reveal malignant cells and polymorphonuclear leucocyte counts above.

Diagnosis

In the great majority of patients ascites is caused by malignant disease, cirrhosis or cardiac failure. However the presence of cirrhosis does not necessarily mean that this is the cause of the ascites. Asciteswith a protein concentration above 25 g/l raises the possibility of infection (especially tuberculosis), malignancy, hepatic venous obstruction, pancreatic ascites or rarely, hypothyroidism.

Management

Restriction of dietary sodium intake is essential to achieving negative Na balance in patients with ascites. Ascitescan be mange with anti-diuretic drugs.

Acute Hepatic Failure

Acute failure is rare syndrome in which hepatic encephalopathy, characterized by mental changes progressing from confusion to stupor and coma.

Causes

Acute liver failure (ALF) is the culmination of severe liver cell injury from a variety of causes including viral hepatitis, toxins, metabolic disorders, and vascular insults. In India, viral hepatitis A and E are the most common cause for ALF. About 15-22% of ALF occur without any identifiablecause.

Wilson's disease accounts for 6-12% of cases of ALF. ALF due to Wilson disease occurs mainly in young females. It should be suspected when patient has very high serum bilirubin and low alkaline phosphatase at presentation. Hemolysis, elevated liver enzymes, low plateletsyndrome, and acute fatty liver of pregnancy are two overlapping syndromes occurring in the second half of pregnancy.

Acute Budd Chiari syndrome can rarely present as ALF. Early recognition and prompt treatment can result in good recovery. Ischemic liver injury occurs in setting of cardiac arrest or intractable hypotension. Here, the aminotransferases will be markedly elevated and responds dramatically to stabilization of circulatory problem.

Acute liver failure occurs in <20% of autoimmune hepatitis. Presence of autoantibodies and a compatible picture on biopsy helps to make a diagnosis. Amanita Phalloides mushrooms, heat stroke, and malignant infiltration of the liver are rare causes of liverinjury.

Pathology

Extensive parenchymal necrosis is the most common histological appearance. Severe fatty degeneration is characteristic of fulminant hepatic failure caused by drugs such as tetracycline, pregnancy and Reye's syndrome.

Clinical Features: Clinical features are reduced alertness and poor concentration, progressing through behavioral abnormalities such as restlessness, aggressive outbursts and mania, to drowsiness and coma.

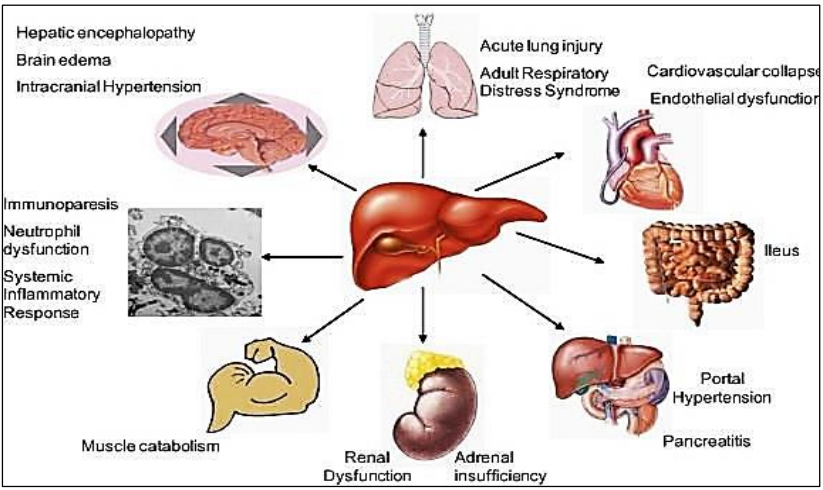


Fig 3: Systemic manifestation of acute liver failure

Investigation

Toxicology screen of blood and urine, IgM anti HBs, IgM anti HAV, anti HEV, cytomegalovirus, herpes simplex, Epstein barr virus, ceruloplasmin, serum copper, urinary copper, ultrasound of liver, Doppler of hepatic veins, chest radiograph, Auto antibodies like ANF, AMA, ASMA, LKM.

Complication

Complication of acute hepatic failure are encephalopathy, cerebral oedema, respiratory failure, hypotension, hypothermia, infection, bleeding, pancreatitis, renal failure, metabolic like hypoglycemia, hypokalemia, hypocalcaemia, hypomagnesaemia, acid base disturbance.

Management

Acute hepatic failure patients should be observed in ICU with clear observation like.

Neurological-conscious level, pupils-size, equality, reactivity, fundi-papilloedema, plantar responses.

Cardiorespiratory-pulse, blood pressure, central venous pressure, respiratory rate.

Fluid balance-input-oral, intravenous and output are hourly urine output, 24 hours sodium output vomiting, diarrhoea.

Blood analyses-peripheral blood count, Creatinine, blood urea, serum electrolytes, calcium, magnesium, glucose, prothrombin time.

Infection surveillance like cultures-blood, urine, throat, sputum, chest radiograph and temperature.

Hepatitis

It is inflammation of the liver which results in damage to hepatocytes with subsequent cell death.

Hepatitis A, B, and C cause acute infection of the liver that may manifest as an acute icteric illness or be detected incidentally as raised transaminase levels.

Hepatitis A Virus

Hepatitis A virus (HAV) is transmitted faeco orally. There is evidence for sexual transmission between homosexual men with several outbreaks reported. The specific risk factors are not well defined but probably relate to

Oro anal or digital rectal contact, particularly in settings such as public saunas and dark rooms. Acute icteric hepatitis appears after an incubation period of 15-45 days, symptoms last for about 6 weeks, and it is only rarely fatal. Infectivity lasts from approximately 2 weeks before the onset of jaundice to 1 week after.

Hepatitis B Virus

Hepatitis B virus (HBV) infection is transmitted vertically (mother to child), parenterally, and sexually. There is a much lower risk to household contacts of acute cases and high infectivity carriers of individuals seen in STD clinics, those at greatest risk of infection are homosexual men and injecting drug users. Acute hepatitis B has an incubation period of 40-160 days with symptoms lasting up to 12 weeks. Fulminant hepatitis occurs in about 1% and may be fatal [6]. About 5% of infected adults are asymptomatic. About 5-10% of immunocompetent patients and up to 40% of immunocompromised patients develop chronic infection. Symptomatic acute infection very rarely leads to chronicity. Infectivity lasts from approximately 2 weeks before the onset of jaundice until the loss of infection markers. Cirrhosis or liver cancer may develop in up to 20% of chronic carriers over 10-50years.

Hepatitis C Virus

Hepatitis C virus (HCV) is transmitted parenterally although there is a low rate of sexual and vertical transmission, which is more likely to occur within the setting of HIV/HCV co-infection. Them ajority (60-70%) develop chronic infection. As with HBV infection, cirrhosis and liver cancer ensue in 20% or more over the next 10-50 years.

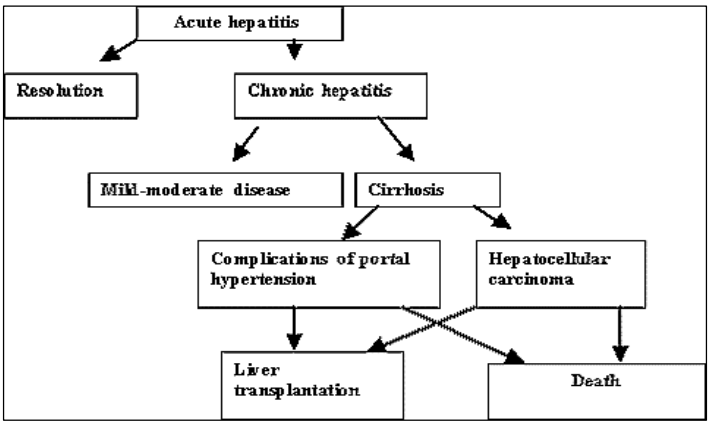


Fig 4: Flow chart of Hepatitis

Clinical Features

Symptoms of hepatitis are fatigue, flu like symptoms, dark urine, pale stool, abdominal pain, loss of appetite, yellow skin and eyes, weight loss, anorexia and difficulty in concentration. Severe hepatitis may be associated with encephalopathy, increasing jaundice and prolongation of the prothrombin time.

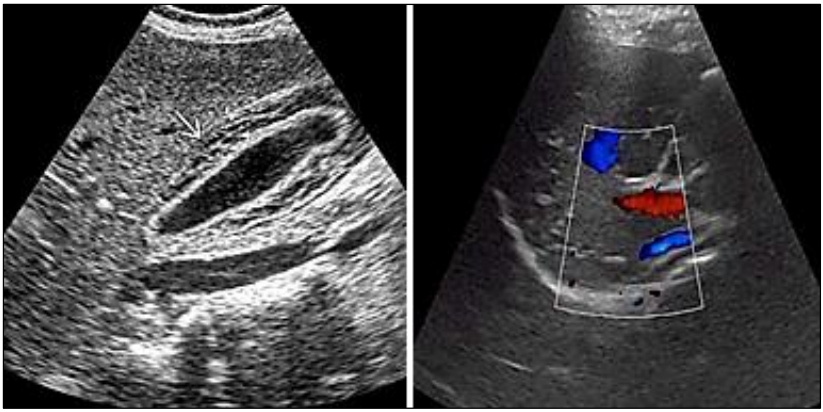


Fig 5: Ultrasound finding of hepatitis

Cirrhosis of the Liver

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and end stage liver disease.

Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, resulting in improved management, quality of life and life expectancy of cirrhotic patients.

Etiology

Cirrhosis of the liver causes are any cause of chronic hepatitis, alcohol, primary biliary cirrhosis, primary sclerosing cholangitis, secondary biliary cirrhosis (stone, strictures), haemochromatosis, wilson's disease, alpha 1 antitrypsin deficiency.

Pathophysiology

Fibrosis describes encapsulation or replacement of injured tissue by a collagenous scar. Liver fibrosis results from the perpetuation of the normal wound healing response resulting in an abnormal continuation of fibrogenesis (connective tissue production and deposition). Fibrosis

progresses at variable rates depending on the cause of liver disease, environmental and host factors. Cirrhosis is an advanced stage of liver fibrosis that is accompanied by distortion of the hepaticvasculature.

It leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma, i.e., hepatocytes. The hepatic sinusoids are lined by fenestrated endothelia which rest on a sheet of permeable connective tissue (the space of Disse) which contains hepatic stellate cells (HSC) and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes which execute most of the known liver functions. In cirrhosis the space of Disse is filled with scar tissue and endothelial fenestrations are lost, a process termed sinusoidal capillarization. Histologically, cirrhosis is characterized by vascularized fibrotic septa that link portal tracts with each other and with central veins, leading to hepatocyte islands that are surrounded by fibrotic septa and which are devoid of a central vein. The major clinical consequences of cirrhosis are impaired hepatocyte (liver) function, an increased intrahepatic resistance (portal hypertension) and the development of hepatocellular carcinoma (HCC). The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are intimately linked to the hepatic vascular alterations and the resulting portal hypertension.

Cirrhosis and its associated vascular distortion are traditionally considered to be irreversible but recent data suggest that cirrhosis regression or even reversal is possible.

Clinical Features

Cirrhosis of the liver symptoms are weakness, fatigue, muscle cramps, weight loss, anorexia, nausea, vomiting, upper abdominal discomfort, gaseous abdominal distension, hepatomegaly, jaundice, ascites, spider telangiectasia, palmar erythema, cyanosis, loss of llibido, hair loss, bruises, purpura, epistaxis, menorrhagia, splenomegaly, collateral vessels, variceal bleeding, fetor hepaticus, pigmentation, digital clubbing, low grade fever. In endocrine changes in men are gynaecomastia, testicular atrophy, impotence and for females are breast atrophy, irregular menses, amenorrhea.

Investigation

Ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI) are not sensitive to detect cirrhosis, and final diagnosis still relies onhistology.

However, their specificity is high when an obvious cause is present and imaging reveals an inhomogeneous hepatic texture or surface, rarefied hepatic central vein, an enlarged caudate lobe, splenomegaly or collateral veins. Ultrasonography and Doppler ultrasonography of portal and central vein diameters and velocities are useful screening tests for portal hypertension and vessel patency. *Contrast ultrasonography examines* the appearance of echogenic microbubbles in the hepatic vein. *Elasticity measurement* (Fibroscan) is a promising technique based on the velocity of an elastic wave via an intercostally placed transmitter. Liver biopsy is considered the gold standard for diagnosis of cirrhosis, and sequential histological *grading* of inflammation and *staging* of fibrosis can assess risk of progression. A liver biopsy is obtained by either a (radiographically guided) percutaneous, a transjugular or laparoscopic route. A greater risk of bleeding following a biopsy has been observed with larger diameter needles.

Complications

Cirrhosis of liver complications is variceal bleeding, ascites and renal failure.

Chapter - 8

Diseases of the Connective Tissues

Lumbar Spondylosis

It is defined as a "degenerative changes in the discs and lumbar spine are almost universal in the elderly" (or) is a chronic, noninflammatory disease caused by degeneration of lumbar disc and/or facet joints. Its affects approximately 60-85% of adults during some point in their lives. Fortunately, for the large majority of individuals, symptoms are mild and transient, with 90% subsiding within 6 weeks. Pain, defined as pain symptoms persisting beyond 3 months, affects an estimated 15-45% of the population. Degenerative spine changes are remarkably common in population studies. Symmons' *et al*. Study of individuals aged 45-64 years identified 85.5% of participants to demonstrate osteophytes within the lumbar spine. O'Neill *et al*. explored osteophytosis within a UK adult population over age 50 years, finding 84% of men and 74% of women to demonstrate at least one vertebral osteophyte, with increased incidence among individuals with more physical activity, self-reported back pain, or higher BMI scores. Despite marked variability within the population, men appear to have more significant degenerative changes than women, both with regard to number and severity of osteophyteformation.

Causes

Age: An extensive autopsy study in 1926 reported evidence of spondylitis deformans to increase in a linear fashion from 0% to 72% between the ages of 39 and 70 years.

Hereditary

Genetic factors likely influence the formation of osteophytes and disk degeneration. Spector and MacGregor proposed that 50% of thevariability found in osteoarthritis can be attributed to heritable factors. Similarly, twin studies evaluating the progression of degenerative changes in lumbar MRI imaging suggest that approximately half (47-66%) of the variance could be explained by genetic and environmental factors, attributing only 2-10% of variance to physical loading and resistance training.

Occupation: Disk generation has long been associated with certain activities.

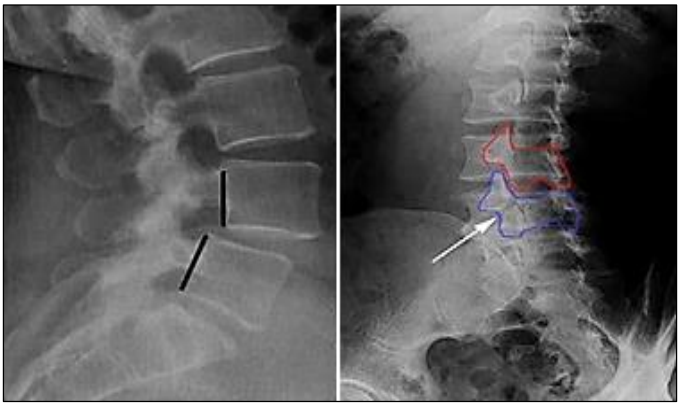


Fig 1: Lumbar Spondylosis

Pathogenesis

The high incidence of simultaneous degenerative changes to the intervertebral disk, vertebral body, and associated joints suggests a progressive and dynamic mechanism, with interdependent changes occurring secondary to disk space narrowing.

Phase I (Dysfunction Phase): It describes the initial effects of repetitive microtrauma with the development of circumferential painful tears of the outer, innervated anulus, and associated end-plate separation that may compromise disk nutritional supply and waste removal. Such tears may coalesce to become radial tears, more prone to protrusion, and impact the disk's capacity to maintain water, resulting in desiccation and reduced disk height. Fissures may become ingrown by vascular tissue and nerve endings, increasing innervation and the disk's capacity for pain signal transmission.

Phase II (Instability Phase): It is characterized by the loss of mechanical integrity, with progressive disk changes of resorption, internal disruption, and additional annular tears, combined with further facet degeneration that may induce subluxation and instability.

Phase III (Stabilization Phase): It continued disk space narrowing and fibrosis occurs along with the formation of osteophytes and transdiscal bridging.

Schneck presents a further mechanical progression, building upon this degenerative cascade of the intervertebral disk, to explain other degenerative changes of the axial spine. He proposes several implications of disk space

narrowing. Adjacent pedicles approximate with a narrowing of the superior inferior dimension of the intervertebral canal. Laxity due to modest redundancy of the longitudinal ligaments enables bulging of the ligamentum flavum and potential for spine instability. Increased spine movement permits subluxation of the superior articular process (SAP), causing a narrowed anteroposterior dimension of the intervertebral and upper nerve root canals. Laxity may also translate into altered weight mechanisms and pressure relationships on vertebral bone and joint spaces believed to influence osteophyte formation and facet hypertrophy to both inferior and superior articular processes with risks for projection into the intervertebral canal and central canal, respectively. Oblique orientations of the articular processes may further cause retrospondylolisthesis, with resulting anterior encroachment of the spinal canal, nerve root canal, and intervertebral canal.

Clinical Features

Postural low back pain is often provoked by prolonged sitting, standing, bending or lifting. Acute episodes with symptoms and signs of nerve root compression are similar to those following acute disc prolapsed.

Investigations

Imaging tests can provide detailed information to guide diagnosis and treatment.

- **Neck X-Ray:** An X-ray can show abnormalities, such as bone spurs, that indicate cervical spondylosis. Neck X-ray can also rule out rare and more serious causes for neck pain and stiffness, such as tumors, infections or fractures.
- **CT scan:** A CT scan can provide more detailed imaging, particularly of bones.
- **MRI:** MRI can help pinpoint areas where nerves might bepinched.
- **Myelography:** A tracer dye is injected into the spinal canal to provide more detailed X-ray or CTimaging.
- **Electromyography:** This test measures the electrical activity in your nerves as they transmit messages to your muscles when the muscles are contracting and atrest.
- **Nerve Conduction Study:** Electrodes are attached to your skin above the nerve to be studied. A small shock is passed through the nerve to measure the strength and speed of nervesignals [3].

Osteoarthritis

Osteoarthritis also called as degenerative joint disease. It involved more than one disease. Osteoarthritis is the clinical and pathological outcome of a range of disorders that results in structural and functional failure of synovial joints. Traditionally, it has been considered a disease of articular cartilage. The current concept holds that osteoarthritis involves the entire joint organ, including the subchondral bone, menisci, ligaments, periarticular muscle, capsule, and synovium. Osteoarthritis is the most prevalent form of arthritis, with an associated risk of mobility disability (defined as needing help walking or climbing stairs) for those with affected knees being greater than that due to any other medical condition in peopleaged.

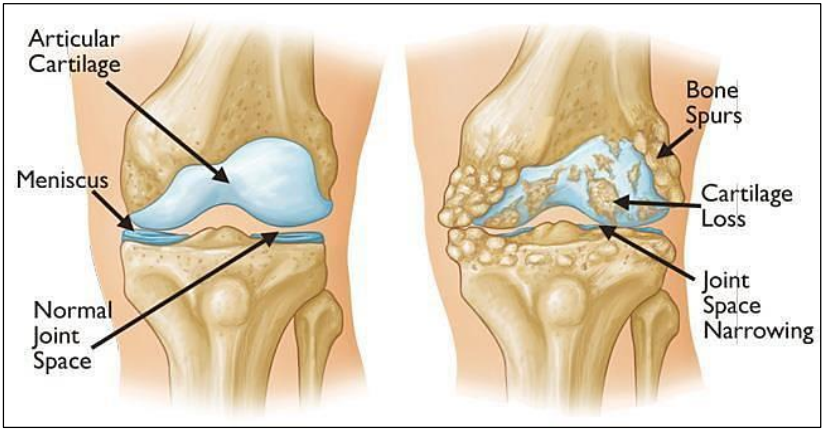


Fig 2: Normal knee and Osteoarthritis knee

Osteoarthritis is classified into Two Groups

Primary osteoarthritis can be localised or generalised, the latter more commonly found in postmenopausal women, with development of Heberden's nodes. Secondary osteoarthritis has an underlying cause, such as trauma, obesity, Paget's disease, or inflammatory arthritis.

Causes: osteoarthritis etiology is unknown and degenerative joint changes occur in response to a recognizable local or systemic factor. In developmental causes are perthes diseases, slipped capital femoral epiphysis, epiphysiolysis, hip dysplasia, epiphyseal dysplasias, intra articular acetabular labrum. Traumatic causes are intra articular fracture, meniscectomy, occupational e.g. elbows of pneumatic drill operators, hypermobility e.g. Ehlers danlos syndrome, long leg arthropathy. Metabolic causes are alkaptonuria (ochronosis), haemochromatosis, Wilson's disease,

chondrocalcinosis. Inflammatory causes are rheumatoid arthritis, gout, septic arthritis, haemophilia. Aseptic necrosis are corticosteroids, sickle cell disease, decompression sickness, SLE and other collagenesis. In neuropathic causes are tabes dorsalis, syringomyelia, diabetes mellitus, peripheral nerve lesions. In endocrine is acromegaly and Paget's disease, gaucher'sdisease.

Pathogenesis

Cartilage is made of water (70%) and a type II collagen framework with proteoglycans and glycosaminoglycans (consisting mainly of aggrecan and also chondroitin), produced by chondrocytes. Proteoglycans in turn bind to hyaluronate which stabilize the macromolecule. Chondrocytes receive nutrition from the synovium by diffusion and the synovial fluid is circulated by joint movement. It has been postulated that if the joint stops moving (as a result of a fracture or immobility) and chondrocytes lose their source of nutrition, they go into shock and cartilage repair ceases. Metalloproteinases are produced, which catalyse collagen and proteoglycan degradation. The synovium has been shown to be variably inflamed in osteoarthritis producing increased levels of inter leuk in-1(IL-1) and tumour necrosis factor-alpha (TNF-α), cytokines that induce nitric oxide and metalloproteinase production. Interleukin-6 (IL-6) and mechanical loading of the joint also induce catabolic cytokine receptors. These bind IL-1 and TNF-α within cartilage causing more destruction. It is thought that the osteophytes and subchondral sclerosis seen in osteoarthritis may be the body's way of trying to compensate for lack of cartilage, although some researchers have found bony changes before cartilage changes in animal models. This sort of abnormal bone is also thought to lead to further degradation of the cartilage surrounding it. Poor synthesis of cartilage building blocks may be caused by dysfunctional forms of insulin like growth factor-1 and transforming growth factor beta, agents which normally promote new cartilageformation.

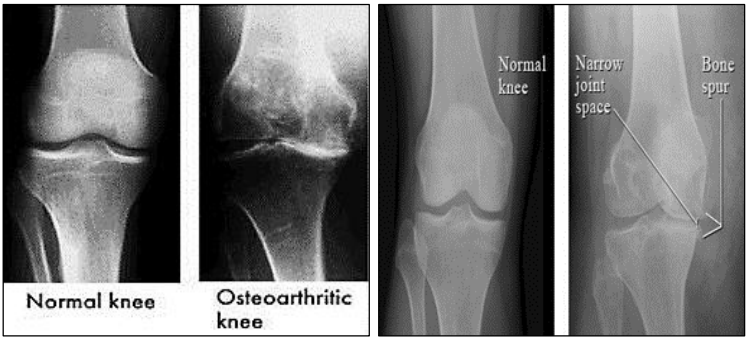


Fig 3: X-ray normal knee and osteoarthritis knee

Clinical Features

Osteoarthritis most frequently involved are those of the spine, hips, knees and hands. Common patterns of joint involvement include the nodal and non-nodal types of primary generalized osteoarthritis with prominent involvement of the knee and hands (distal interphalangeal joints, proximal interphalangeal joints, carpometacarpal joints of thumbs), as well as osteoarthritis confined to the knee or hips. All symptoms are gradual in onset. Pain is at first intermittent and is provoked by the use of the joint and relieved by rest. As the disease progresses, movement in the affected joint becomes increasingly limited, initially as a result of pain and muscular spasm, but later because of capsular fibrosis, osteophyte formation and remodeling of bone.

Muscle wasting is an important factor in the progress of the disease, as in the absence of normal muscular control the joint becomes more prone to injury. Nodal osteoarthritis occur predominantly in middle aged women. It affects the terminal interphalangeal joints of the fingers, with the development of gelatinous cysts or bony out growths on the dorsal aspect of these joints (Heberden's nodes, see fig.4). The onset is sometimes acute, with considerable pain, swelling and inflammation.

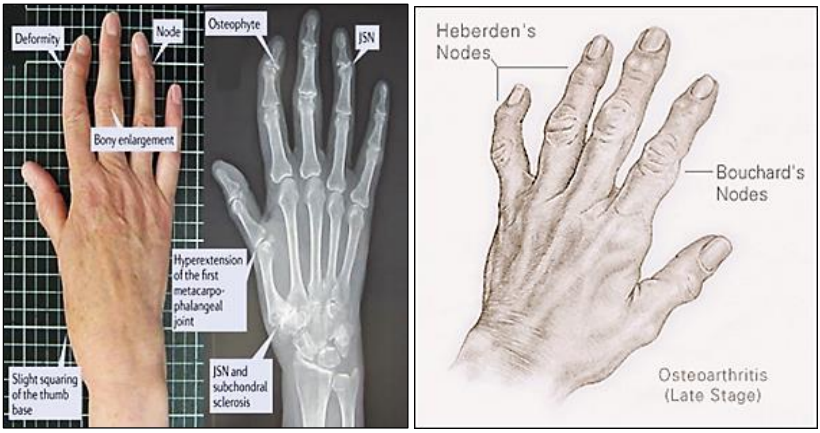


Fig 4: Nodal osteoarthritis

Heberden's nodes seldom cause serious disability. Similar lesions may affect the proximal interphalangeal joints (Bouchard's Nodes) (figure 4), and the disorder also frequently involves the carpometacarpal joints of the thumbs, the spinal apophyseal joints, the hips and the knees.

Investigation

The blood count and ESR are characteristically normal. Several radiograph scoring systems have been employed to assist the measurement of osteoarthritis progression. Other techniques include chondrometry, where minimal inter bone distance is measured using a special compass magnifying glass calibrated to 0.1 mm. Synovial fluid is viscous and has a low cellcount.

Plain Radiographs: The following changes may be seen on plain radiographs: Joint space narrowing, Osteophytes, bony cysts and sub chondral sclerosis.

M.R.I

This is already well established for use in assessing ligament and meniscal tears in the knee. It has no place in routine clinical assessment of osteoarthritis, but may be a specific and sensitive way of quantifying cartilage loss. Currently, magnetic resonance imaging has not proved to be sensitive enough in the detection of preclinical osteoarthritis. Changes in surface morphology and full thickness cartilage defects can be seen, but fibrillation cannot yet be evaluated.

Management

Weight loss-Encourage overweight patients with osteoarthritis of the hip and knee to lose weight through a combination of diet and exercise.

Physical therapy consists of several strategies to facilitate resolution of symptoms and improve functional deficits, including range of motion exercise, muscle strengthening, muscle stretching, and soft tissue mobilisation.

Knee braces and orthotics-For those with instability of the knee and varus misalignment, valgus bracing and orthotics shift the load away from the medial compartment and, in doing so, may provide relief of pain and improvement in function.

GOUT

Gout is a picturesque presentation of uric acid disturbance. It is the most well understood and described type of arthritis. Gout is a systemic disease that results from the deposition of monosodium urate crystals (MSU) in tissues. Increased serum uric acid (SUA) above a specific threshold is a requirement for the formation of uric acid crystals. Despite the fact that hyperuricemia is the main pathogenic defect in gout, many people with hyperuricemia do not develop gout or even form UA crystals. In fact, only

5% of people with hyperuricemia above 9 mg/dL develop gout. Accordingly, it is thought that other factors such as genetic predisposition share in the incidence of gout. The general prevalence of gout is 1–4% of the general population. In western countries, it occurs in 3–6% in men and 1–2% in women.

In some countries, prevalence may increase up to 10%. Prevalence rises up to 10% in men and 6% in women more than 80 years old. Annual incidence of gout is 2.68 per 1000persons.

Factors Predisposing to Hyperuricemia

Renal failure, drugs (diuretics, low does of aspirin), lead poisoning, hyper parathyroidism, myxoedema, down's syndrome, lactic acidosis (alcohol, exercise, starvation, vomiting, toxaemia of pregnancy, type 1 glycogen storage disease), unidentified inherited defect, myeloproliferative disorder, lymphoproliferative disorder, hypoxanthine, phosphoribosyl pyrophosphate synthetaseoveractivity, glucose 6 phosphate deficiency, idiopathic, Deficiency of enzymes involved in purine metabolism leads to overproduction of UA.

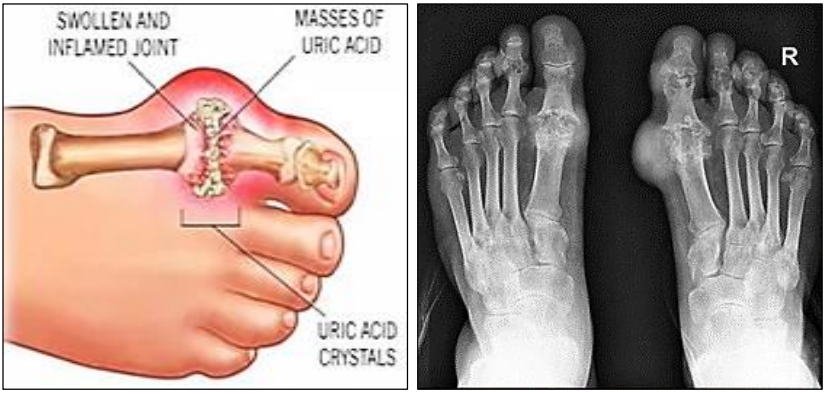


Fig 5: Radiology of the Gout

Pathophysiology

Urate is the ionized form of uric acid present in the body. Uric acid is a weak acid with pH of 5.8. Urate crystals deposition in tissues starts to occur when serum uric acid level rises above the normal threshold. Pathological threshold of hyperuricemia is defined as 6.8 mg/dl. Some factors may affect the solubility of uric acid in the joint. These include synovial fluid pH, water concentration, electrolytes level, and other synovial components such as proteoglycans and collagen.

SUA level in the body is determined by the balance between its production either from purine intake in diet or endogenous production by cellular turnover and its excretion by the kidneys and GIT. Increased production of UA is responsible for only 10% of cases of gout while the remaining 90% are caused by its renal under excretion. Factors affecting SUA levels include age and gender. SUA is low in children. After puberty, SUA levels start to increase to reach their normal levels. In men, levels are higher than in women. However, SUA levels in postmenopausal women increase to reach men's levels. This explains why gout is usually a disease of middle aged and older men, and postmenopausal women. Rarely, it may happen in children and young adults in some rare inborn errors of purine metabolism. These enzymatic defects result in increased SUA with consequent production of UA crystals in kidneys andjoints.

Clinical Features

The ankle, knee, small joints of the feet and hands, writs, elbow follow in decreasing order of frequency. The onset may be insidious or explosively sudden, often waking the patient from sleep. The effected joint in hot, red, swollen with shiny overlying skin and dilated veins, painful and tender.

Investigation

The serum urate level is usually raised but it is important to appreciate that this does not prove the diagnosis because asymptomatic hyper uricaemia is very common. Among patients with SUA levels between 7 and 7.9 mg/dL only 0.09% will develop gout every year. As for patients with SUA between 8 and 8.9 mg/dl, 0.4% out of them may develop gout. With hyperuricemia above 9 mg/dl, only 0.5% of patients may get gout. The gold standard of diagnosis is the identification of MSU crystals in synovial fluid aspirate using polarized light microscopy. In chronic tophaceous gout, the main radiographic features are:

- Tophi which are articular or periarticular soft tissue densenodules
- MSU deposits in the cartilaginouspart
- Joint space narrowing in advanceddisease
- Bone erosions are characteristic. They are well circumscribed intra-articular or juxta articular lesions with overhanging margins. They result from the growth of tophi into the bone, hence are usually seen neartophi
- Periarticular osteopenia is usually absent and proliferating bone can be seen mostly as irregularspicules

Doppler US can distinguish between active/hot tophi and inactive/cold ones based on their Doppler signal. Conventional CT is not helpful in the diagnosis of acute gout as it can't detect inflammation, synovitis, tenosynovitis and osteitis. This handicap is however, more than counterbalanced by its role in chronic gout. It is able to detect erosions better than Magnetic Resonance Imaging (MRI) or CR. Nuclear Scintigraphy is rarely used for evaluation. Positive results are often found incidentally when a study is performed for other indications.

Rheumatoid Arthritis

It is the most common form of chronic inflammatory joint disease. Rheumatoid arthritis (RA) is an inflammatory rheumatic disease with progressive course affecting articular and extra-articular structures resulting in pain, disability and mortality. Persistent inflammation leads to erosive joint damage and functional impairment in the vast majority of patients. The course of disease may be also different according to the presence or absence of several variables including genetic background, frequency of swollen joints, autoantibody in the serum and the severity of inflammatory process. The initial presenting features of early RA do not substantially differ from other inflammatory arthritis. So prior to definite diagnosis patients with early RA are usually classified as undifferentiated arthritis which difficultly can be discriminated from other inflammatory arthritis. Up to now, early RA was denoted to patients with disease duration of less than 2 years preferentially less than 12 months but currently most rheumatologists are willing to see the patients with symptom duration of less than 6 weeks. At present, "early" rheumatoid arthritis is regarded as patients with symptom duration <3 months as early disease.

Rheumatoid arthritis can involve most synovial joints, but rarely the DIPs or the thoracic, lumbar and sacral spine. The most commonly affected joints include the MCP and PIP joints of the hands, wrists and MTP joints of the feet. Joint destruction begins early in the disease with erosive changes often seen after only six months. The clinical exam can disclose synovial thickening and swelling, indicators of joint inflammation.

Causes

Some people appear to have genetic factors that make it more likely. One theory is that bacteria or a virus triggers RA in people who have this genetic feature. In RA, the immune system's antibodies attack the synovium, which is the smooth lining of a joint. When this happens, pain and inflammation result. Inflammation causes the synovium to thicken.

Eventually, if left untreated, it can invade and destroy cartilage-the connective tissue that cushions the ends of the bones. The tendons and ligaments that hold the joint together can also weaken and stretch.

The joint eventually loses its shape and configuration. The damage can be severe.

Pathophysiology

The earliest changes are swelling and congestion of the synovial membrane and the underlying connective tissues, which become infiltrated with lymphocytes (especially CD4 T cells), plasma cells and macrophages. Effusion of synovial fluid in to the joint space takes place during active phases of the disease. Hypertrophy of the synovial membrane occurs, with the formation of lymphoid follicles resembling an immunologically active lymph node. Inflammatory granulation tissue (pannus) spread over and under the articular cartilage, which is progressively eroded and destroyed. Latterly, fibrous or bony ankylosis may occur. Muscles adjacent to inflamed joints atrophy and there may be focal infiltration with lymphocytes. Subcutaneous nodules consist of a central area of fibrinoid material surrounded by a palisade of proliferating mononuclear cells. Similar granulomatous lesions may occur in the pleura, lung, pericardium and sclera. Lymph nodes are often hyperplastic, showing many lymphoid follicles with large germinal centres and numerous plasma cell in the sinuses and medullarycords.

Immunofluorescence show that the plasma cells in the synovium and lymph nodes synthesis rheumatoid factors.

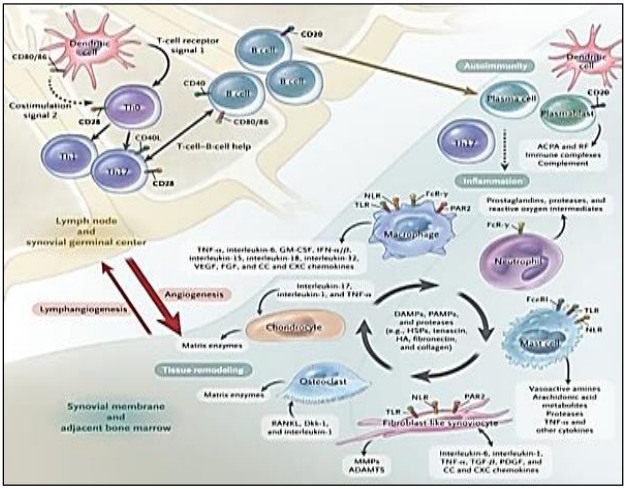


Fig 6: Pathology of rheumatoid arthritis

Clinical Features

Early symptoms of rheumatoid arthritis may appear as vague pain with gradual appearance without classic symptoms of joint swelling or tenderness. These unusual symptoms are usually non-specific, and may persist for prolong period. Early articular manifestations of rheumatoid arthritis may be indistinguishable from other rheumatic diseases. Prolong duration of morning stiffness with arthralgia, or arthritis in a limited number of joints may be a clue for considering rheumatoid arthritis diagnosis. Involvement of small joints of the hands or feet with swelling and tenderness particularly symmetric pattern of involvement along with positive compression test is highly suggestive of rheumatoid arthritis.

Fig 7: The hand in rheumatoid arthritis

Presence of some clinical features such as polyarthritis, symmetric arthritis,hand arthritis, pain upon squeezing the metacarpophalangeal or metatarsophalangeal joints, and morning stiffness greater than 30 minutes can be helpful not only in estimating the future course of arthritis but also in limiting the spectrum of differential diagnosis. Identification of all involved joints by precise clinical examination is essential. Counting the tender and swollen joints, and calculation of disease activity score are logical methods for the determination of disease severity and response to treatment. In rheumatoid arthritis will be there swan neck deformity of the hands, wasting of the small muscles of the hands and synovial swelling at the writs, the extensor tendon sheaths, the metacarpophalangeal and proximal interphalangeal joints (figure 7).

Extra Articular Manifestation of Rheumatoid Arthritis

Extra articular manifestation of rheumatoid arthritis are fever, weight loss, fatigue, susceptibility to infection. In musculo skeletal are musclewasting, tenosynovitis, bursitis, osteoporosis. In haematological are anaemia, thrombocytosis, eosinophilia. Vasculitis are digital arteritis, ulcers,

pyoderma gangrenosum, mononeuritis multiplex, visceral arteritis. In cardiac are pericarditis, myocarditis, endocarditis, conduction defects, coronary vasculitis, granulomatous aortitis. In pulmonary system are nodules, pleural effusion, fibrosing alveolitis, bronchiolitis, captain's syndrome. In neurological system are cervical cord compression, compression neuropathies, peripheral neuropathy, mononeuritis multiplex and also amyloidosis.

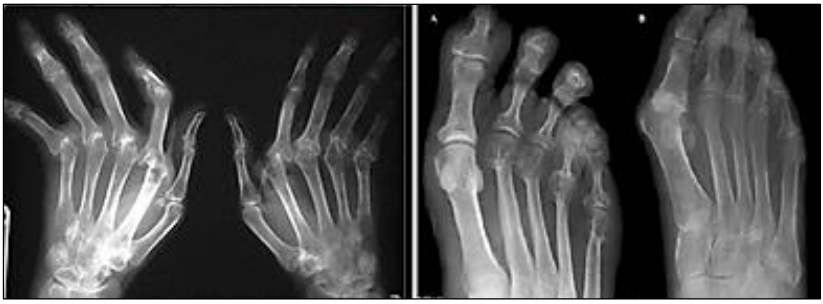


Fig 8: Radiological feature of rheumatoid arthritis

Subcutaneous nodules occur in about 20% of patients. They are usually seen at sites of pressure of friction, such as the extensor surfaces of the forearms below the elbow, bilateral posterior of the ankle joint (figure 9).

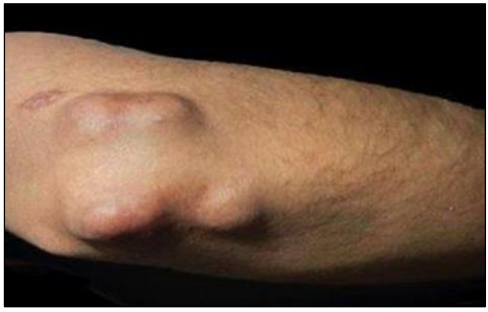


Fig 9: Rheumatoid nodules

Air Way Manifestation

The presence of airway disease in RA is estimated to affect 20-30% of patients. Manifestations can include cricoarytenoid arthritis, pulmonary fibrosis and small airway disease, typically seen as bronchiolitis obliterans on histopathology, with obstructive abnormalities on lung function testing. Lung disease is more frequent in RA patients who are male, seropositive, smoke, and have longstanding disease. Some types of RA-associated lung disease are steroid responsive, but some patients have a progressive course

leading to end-stage fibrosis and death. In addition to lung disease secondary to RA, patients are also at risk for pulmonary toxicities from RA-related medications, including methotrexate, leflunomide and even anti-TNFmedications.

Cardiac Vascular System Manifestation

Rheumatoid arthritis patients have a 40% increased risk of mortality as compared to the general population after 20 years of disease. This increased risk of mortality is primarily attributed to an increased incidence of cardiovascular disease. The propensity for vascular changes is found even in newly diagnosed patients, indicating that common mechanisms may exist linking synovitis resulting in joint destruction with endothelial dysfunction resulting in atherosclerosis.

Bone Manifestation

The bones of rheumatoid arthritis patients are affected in both a local and systemic manner. At a local level, factors that stimulate osteoclasts resulting in increased bone resorption are released from inflammatory and fibroblastic pannus cells. Additionally, inflammatory cytokines prevent a compensatory increase in the rate of periarticular bone formation, resulting in net bone loss. This inhibition of osteoblastic activity is via a combination of impaired mineralization and impaired osteoblast differentiation. Bony changes in rheumatoid arthritis patients are not only seen in a periarticular distribution. Rheumatoid arthritis is a known risk factor for osteoporosis, with up to 30% of patients affected by some estimates. The risk of osteoporosis in rheumatoid arthritis patients is greater at the femoral neck than in the spine, but both areas can be involved.

Investigations

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) provide the best information about the acute phase response. The level of CRP was shown to be significantly correlated with the severity of disease as well as radiographic changes. Auto antibodies such as rheumatoid factor and anti-CCP are very helpful for the diagnosis of rheumatoid arthritis. Anti-CCP antibody demonstrated a comparable sensitivity but a greater specificity than rheumatoid factor for the diagnosis of rheumatoid arthritis.

Radiographic signs of rheumatoid arthritis such as joint space narrowing, erosions and subluxation develop at later stage of rheumatoid arthritis process. Plain radiography is the standard method in investigating the extent of anatomic changes in rheumatoid arthritis patients. However,

there are few data regarding the value of conventional radiographic examination in recent onset arthritis. Synovitis is the early findings of rheumatoid arthritis and is strong predictor of bone erosion. Soft tissue swelling and mild juxtaarticular osteoporosis may be the initial radiographic features of hand joints in early-rheumatoid arthritis. Sonography is also a reliable technique that detects more erosions than radiography especially in early rheumatoid arthritis. In early rheumatoid arthritis, sonography can detect greater number of erosions and in a greater number of patients than canradiography.

Complications

Septic arthritis may complicate rheumatoid arthritis, particularly in patient with long standing nodular seropositive disease.

Sjogren's Disease

This is an autoimmune disorder, characterized by lymphocytic infiltration of the salivary and lacrimal gland leading to xerostomia and kerato conjunctivitis sicca. Primary Sjogren's syndrome: age of onset in between 40 to 60, male are more than females, HLA-B8/DR3.

Clinical Features

Common clinical features of primary Sjogren's syndrome is keratoconjunctivitis sicca, xerostomia, salivary gland enlargement and rare clinical manifestations are anaemia, leucopenia, thrombocytopenia, lymphadenopathy, lymphoreticular, malignancy.

Hepatomegaly, malignancy, hepatomegaly, hyperglobulinemic, purpura, vasculitis, neuropathy, myositis, fibrosing alveolitis, glomerulonephritis, renal tubular acidosis.

Secondary sjogren's disease is age of onset 40 -60 age, male are more than females. Common clinical features are mild kerato conjunctivitis sicca, dry mouth, and other associated auto immune disorders are systemic lupus erythematosus, progressive systemic, sclerosis, primary biliary cirrhosis, chronic active hepatitis, polymyositis, thyroiditis.

Investigations

The salivary flow rate is reduced and reduction in lacrimal secretion can be demonstrated by sue of the schirmer teartest.

Reiter's Disease

It is the triad of non-specific urethritis, conjunctivitis and reactive arthritis that follows bacterial dysentery or exposure to sexually transmitted

infection. In 1916, Hans Reiter described the classic triad of arthritis, nongonococcal urethritis, and conjunctivitis (Reiters syndrome, RS) in a Prussian soldier with diarrhea, during the First World War.

Clinical Features

Symptoms generally appear within 1-3 weeks but can range from 4-35 days from onset of inciting episode of urethritis/ cervicitis or diarrhea. Signs and symptoms usually remit within 6 months. However, a significant percentage of patients have recurrent episodes of arthritis (15-50%), and some patients develop chronic arthritis (15-30%). Cardiac signs such as aortic regurgitation caused by inflammation of aortic wall and valve are rare. Other rare manifestations are central or peripheral nervous system lesions and pleuro pulmonary infiltrates.

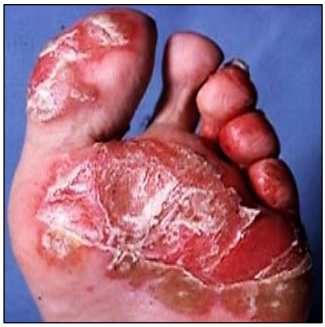


Fig 10: Reiter's disease

It is triggered by bacterial infection that enters via mucosal surfaces usually, (but not always) associated with human leukocyte antigen (HLA)-B27. The syndrome was the first rheumatologic disease noted in association with Human Immunodeficiency Virus. It is most common in individuals aged between 15-35 years; and it is rarely seen in children. The male-to-female post venereal ratio is 5-10:1, while the post-enteric ratio is 1:1. The incidence is estimated at 3.5 per 100,000, and is uncommon among Negroes.

Investigations

The ESR is often raised during the acute phase and may remain so long after joint symptoms have settled. The synovial fluid has the characteristics of a low viscosity inflammatory effusion with leucocyte counts as high as 50000/mm^3 but it is sterile onculture.

Osteoporosis

Osteoporosis, defined as low bone mass leading to increased fracture risk, is a major health problem that affects approximately 10 million world people.

Osteoporosis is characterized by low bone mass, structural deterioration, and porous bone, which are associated with higher fracture risk. Bone loss related to declining estrogen levels increases fracture risk in postmenopausal women, who make up the majority of osteoporosis cases. Screening and diagnosis use a bone mineral density (BMD) measurement that estimates bone strength. Osteoporosis is the most common bone disease in humans, representing a major public health problem. It is more common in Caucasians, women, and older people. Osteoporosis is a risk factor for fracture just as hypertension is for stroke. Osteoporosis affects an enormous number of people, of both sexes and all races, and its prevalence will increase as the population ages. It is a silent disease until fractures occur, which causes important secondary health problems and evendeath.

It was estimated that the number of patients worldwide with osteoporotic hip fractures is more than 200 million. Osteoporosis is also an important health issue in Turkey, because the number of older people is increasing. The incidence rate for hip fracture increasesexponentially with age in all countries as well as in Turkey, which is evident in the fracturk study.

Bone tissue is continuously lost by resorption and rebuilt by formation; bone loss occurs if the resorption rate is more than the formation rate. The bone mass is modeled (grows and takes its final shape) from birth to adulthood: bone mass reaches its peak (referred to as peak bone mass (PBM) at puberty; subsequently, the loss of bone mass starts. PBM is largely determined by genetic factors, health during growth, nutrition, endocrine status, gender, and physical activity. Bone remodeling, which involves the removal of older bone to replace with new bone, is used to repair microfractures and prevent them from becoming microfractures, thereby assisting in maintaining a healthy skeleton. Menopause and advancing age cause an imbalance between resorption and formation rates (resorption becomes higher than absorption), thereby increasing the risk of fracture.

Causes

Osteoporosis causes are genetic (low body weight, family history), endocrine (hypogonadism, early menopause, thyrotoxicosis, hyperparathyroidism), gastro intestinal disease (inflammatory bowel disease, malabsorption, chronic liver disease), inflammatory disease (ankylosing spondylitis, rheumatoid arthritis), inherited (homocystinuria, gaucher's disease, osteogenesis imperfecta), life style (diet/calcium intake, exercise/ immobility, high trained athletes), other are anorexia nervosa, myeloma, neoplasia, mastocytosis, pregnancy associated, juvenile.

Classification

Osteoporosis can be classified into two main groups by considering the factors affecting bone metabolism:

- Primaryosteoporosis
- Secondaryosteoporosis

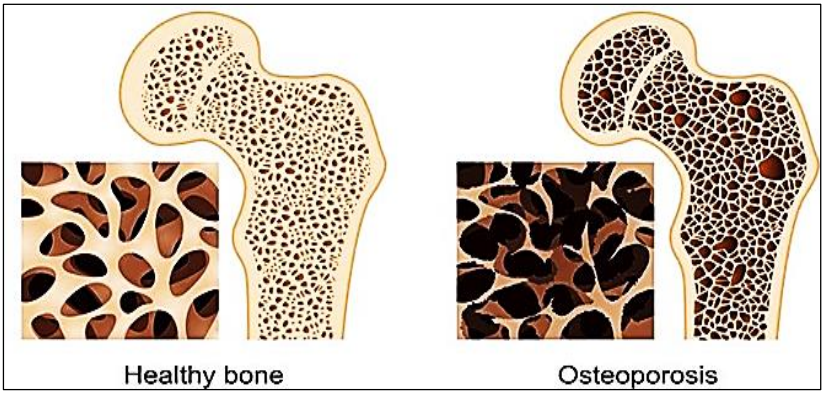


Fig 11: Osteoporosis and health bone

Primary Osteoporosis

It is also known as postmenopausal osteoporosis, caused by the deficiency of estrogen, mainly affecting the trabecular bone; therefore, women are more susceptible to osteoporosis than men, as evident by a men/women ratio of 4/5.7.

Secondary Osteoporosis

It is also called senile osteoporosis, and it is related to bone mass lost due to the aging of cortical and trabecular bones.

Pathogenesis

Genetic factors are important in the pathogenesis of osteoporosis and family studies suggest that genetic influences account for more than 70% of individual variance in bone mass. The molecular genetic basis by which bone mass is regulated is incompletely defined, but may involve subtle variations in the structure or regulation of genes which are involved in forming bone matrix and regulating bone turnover. Calcium intake is also important in determining the rate of post-menopausal bone loss. It may also occur as a complication of endocrine, inflammatory and neoplastic conditions and drug treatment side effect, substance abuse.

Clinical Features

Osteoporosis is a silent disease until the patient experiences a fracture. A recent fracture at any major skeletal site, such as vertebrae (spine), proximal femur (hip), distal forearm (wrist), or shoulder in an adult older than 50 years with or without trauma, should suggest that the diagnosis of osteoporosis needs further urgent assessment involving diagnosis and treatment [21].

Diagnosis

Osteoporosis screening is based on BMD measurement, usually by DXA, which is then used to predict fracture risk. Hip BMD measurement by DXA is the best predictor of future hip fracture risk. In 2011, Nayak *et al*. demonstrated through modeling analysis that screening for postmenopausal osteoporosis leads to more quality-adjusted life years compared with no screening. In addition, DXA scans were cost effective, especially when treatment was started for women with a T-score of -2.5 or more negative, with screening repeated every 5years.

Chapter - 9

Diseases of the Oncology

Breast Cancer

It is a malignant proliferation of epithelial cells lining the duct or lobules of the breast. Breast cancer is one of the most common cancers in women worldwide, accounting for approximately 570,000 deaths in 2015. Over1.5 million women (25% of all women with cancer) are diagnosed with breast cancer every year throughout the world. Breast cancer is a metastatic cancer and can commonly transfer to distant organs such as the bone, liver, lung and brain, which mainly accounts for its incurability. Early diagnosis of the disease can lead to a good prognosis and a high survival rate. In North American, the 5-year relative survival rate of breast cancer patients is above 80% due to the timely detection of this disease. There're numerous risk factors such as sex, aging, estrogen, familyhistory, gene mutations and unhealthy lifestyle, which can increase the possibility of developing breast cancer. Most breast cancer occurs in women and the number of cases is 100 times higher in women than that in men.

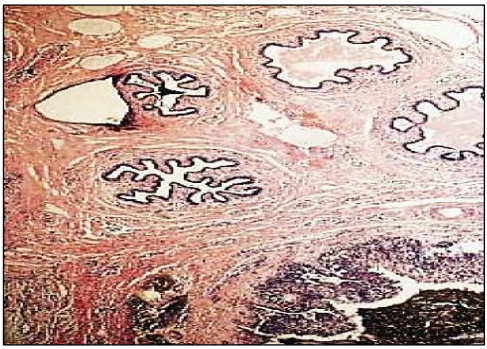


Fig 1: Breast ductal endoscopy

The following are Risk Factors for Breast Cancer

Age: The chances of breast cancer increase as one gets older.

Family History: The risk of breast cancer is higher among women who have relatives with the disease.

Having a close relative with the disease (sister, mother, daughter) doubles w woman's risk.

Personal History: Having a breast cancer diagnosis in one breast increases the risk of cancer in the other breast or the chance of an additional cancer in the originalbreast.

Women diagnosed with certain benign (non-cancerous) breast conditions have an increased risk of breast cancer. These include atypical hyperplasia, a condition in which there is abnormal proliferation of breast cells but no cancer has developed.

Menstruation: Women who started their menstrual cycle at a younger age (before 12) or went through menopause later (after 55) have a slightly increased risk.

Breast Tissue: Women with dense breast tissue (as documented by mammogram) have a higher risk of breast cancer.

Exposure to previous chest radiation or use of diethylstilbestrol increase the risk of breast cancer. Having no children or the first child after age 30 increases the risk of breast cancer. Breast feeding for one and a half to two years might slightly lower the risk of breast cancer. Being overweight or obese increases the risk of breast cancer. Both in pre and postmenopausal women but at different rates. Use of oral contraceptives in the last 10 years increases the risk of breast cancer slightly. Using combined hormone therapy after menopause increases the risk of breast cancer. Alcohol consumption increases the risk of breast cancer and this seems to be proportional to the amount of alcohol used. A recent meta-analysis reviewing the research on alcohol use and breast cancer concluded that all levels of alcohol use are associated with an increased risk for breast cancer. This includes even light drinking. Exercise seems to lower the risk of breast cancer. Breast tumors usually start from the ductal hyperproliferation, and then develop into benign tumors oreven metastatic carcinomas after constantly stimulation by various carcinogenic factors.Tumor microenvironments such as the stromal influences or macrophages play vital roles in breast cancer initiation and progression. The mammary gland of rats could be induced to neoplasms when only the stroma was exposed to carcinogens, not the extracellular matrix or the epithelium. Macrophages can generate a mutagenic inflammatory microenvironment, which can promote angiogenesis and enable cancer cells to escape immunerejection.

Different DNA methylation patterns have been observed between the normal and tumor-associated microenvironments, indicating that epigenetic

modifications in the tumor microenvironment can promote the carcinogenesis.

Recently, a new subclass of malignant cells within tumors called the cancer stem cells (CSCs) are observed and associated with tumor initiation, escape and recurrence. This small population of cells, which may develop from stem cells or progenitor cells in normal tissues, have self-renewal abilities and are resistant to conventional therapies such as chemotherapy and radiotherapy. Signaling pathways including Wnt, Notch, Hedgehog, p53, PI3K and HIF are involved in the self-renewal, proliferation and invasion of bCSCs.

Clinical Features

- A lump in the breast orarmpit
- Bloody nippledischarge.
- Inverted nipple
- Orange peel texture or dimpling of the breast skin (PeauD'orange)
- Breast pain or sorenipple
- Swollen lymph nodes in the neck orarmpit
- A change in the size or shape of the breast ornipple

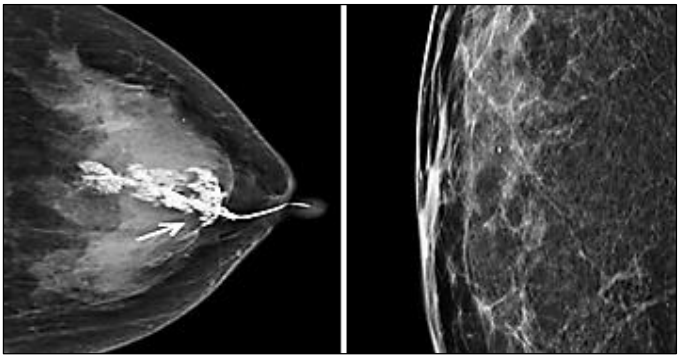


Fig 2: Breast cancer ductal ductography& mammography

Screening

Brest cancer is virtually unique among the epithelial tumors in adults in that screening (in the form of annual mammography) improves survival. Meta-analysis examining out comes from every randomized trial of mammography conclusively shows a more than 25% reduction in the chance of dying from breast cancer with annual screening after age 50 years.

The data for women between ages 40 to 50 are almost as positive. Ductography should be performed precisely, and interpreted meticulously, so as not to miss important signs of breast cancer, and to avoid delayed diagnosis. Previous articles have extensively reviewed ductography techniques, and reported on the nonspecific findings of benign and malignant diseases which can be responsible for nipple discharge. Complete ductal obstruction is not pathognomonic of breast cancer, and can be observed in both benign and malignant tumors. This finding was noted in 5-47% of benign diseases, and in 67-83% of cancers, by ductographyIn approximately 70% of obstructing papillomas, contrast material was observed to partially outline the leading edge of a lesion, resulting in a meniscus-like appearance. By way of contrast, the shape of the cut-off site in the carcinoma on ductography often assumes an irregular, moth eaten appearance (Figure 2). Multiple irregular filling defects in non-dilated peripheral ducts are highly suggestive of malignancy. Shen *et al.* reported on their results with ductoscopy in 415 patients with nipple discharge. They found an intraductal lesion in 166 patients (40%). They found the majority of benign lesions to be present in the main segmental ducts and the first branch while DCIS lesions were situated more peripherally in the first and second branches. The average distance for a DCIS lesion was 3.3 cm, and the most distant lesion was situated 5cm from the nipple. In contrast benign papillomas were situated at an average distance of 2.7 cm and the nearest at 0.5 cm. DCIS lesions were associated with bleeding, circumferential ductal obstruction, and gross fungating projections. The positive predictive value with ductoscopy in detecting DCIS was 80% which increased to 100% when combined with ductal lavage cytology. Dooley evaluated the role of ductoscopy in patients undergoing definite surgery for atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), and breast cancer to assess intra ductal extent of disease and in achieving disease free surgicalmargins.

Management

Breast conserving treatments, consisting of the removal of the primary tumor by some form of lumpectomy with or without irradiating the breast, result in a survival that is as good as for slightly superior to that after extensive surgical procedures, such as mastectomy or modified radical mastectomy with or without further irradiation. The use of systemic therapy after local management of breast cancer substantially improves survival.

More than one third of the women who would otherwise die of metastatic breast cancer remain disease free when treated with the

appropriate systemic regimen. One approach so called neo adjuvant chemotherapy-involves the administration of adjuvant therapy before definitive surgery and radiation therapy. Because the objective response rates of patients with breast cancer to systemic therapy in this setting exceed 75% many patients will be down staged and may become candidates for beast conservingtherapy.

Lung Cancer

The term lung cancer is used for tumors arising from the respiratory epithelium (bronchi, bronchioles and alveoli). Mesotheliomas, lymphomas and stromal tumors are distinct from epithelial lung cancer. Lung cancer is the third most frequently diagnosed cancer in Germany in both men and women. The annual incidence in Germany is 65 per 100 000 for men and 21 per 100 000 for women. The peak incidence is between the ages of 75 and 80 years. At the same time, both in Germany and worldwide, lung cancer is the most frequent cause of death from cancer among men, and in Germany it is the third most frequent cause of death from cancer among women. In men the figures are steady or slightly reducing, but in women the rate is going up. Both incidence and mortality rates reflect cigarette consumption in a given population about 20 years ago. Lung cancer is by far the most common malignant tumor originating in the lung. The four major histological types of lung cancer are:

- Squamous cell carcinoma (30% to 40% of lungcancers)
- Adenocarcinoma (25% to30%)
- Non-small cell lung carcinoma (less than 10%)
- Small cell lung carcinoma (15% to20%)

These four types are subdivided into numerous subtypes. A notable subtype is broncho alveolar carcinoma (synonym: alveolar cell carcinoma), a rare subtype of adenocarcinoma, that lines the alveoli as it grows. Lung cancers can be classified according to a variety of criteria. Histological a distinction is made between small cell lung carcinoma (15% to 20%) and non-small cell lung carcinoma, because of differences in their biological behavior and the implications of these differences for treatment andprognosis.

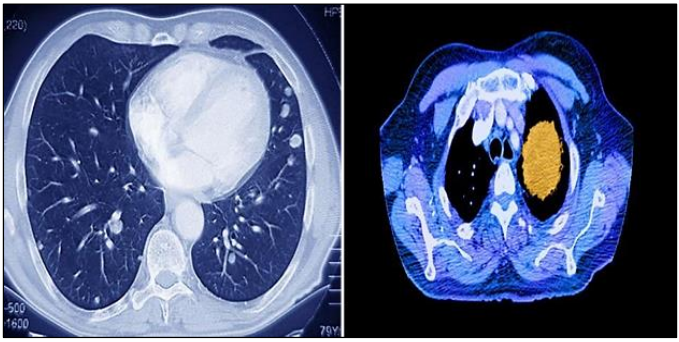


Fig 3: CT scan of Breast cancer of lung & PET

Clinical Features

Cough (8% to 75%), hemoptysis (6% to 35%), pain, wheezing (0% to 2%), poststenotic pneumonia, dyspnea (3% to 60%), stridor (0% to 2%), Chest pain (20% to 49%), hoarseness, upper airway inflow obstruction, Horner's triad, pleural effusion, pericardial effusion, dysphagia, raised diaphragm, Weight loss (0% to 68%), night sweats, fatigue, fever (0% to 20%), Bone pain (6% to 25%), headache, neurological or psychiatric abnormalities, paraplegia, hepatomegaly, pathological fractures, Cushing syndrome, syndrome of inappropriate ADH secretion, Lambert Eaton syndrome, Pierre-Marie-Bamberger syndrome, etc.

Diagnosis

PET/PET-CT imaging is of central importance in tumor staging. Ruling out distant metastases by a negative finding saves further diagnostic procedures, while the detection of structures suggestive of metastasis can guide the next step and move the diagnostic process rapidly forward. In patients in clinical stages IB to IIIB, in whom curative therapy should be attempted, PET/PET-CT scanning (if available) should be carried out for mediastinal N-staging and for M-staging; in stage IA this examination should be considered. In addition to history, clinical exam, and routine laboratory tests, the diagnostic workup of small cell lung cancer should include CT of the chest and abdomen (at least liver and adrenals), bone scintigraphy, and contrast-enhanced cranial CT or cranial MRI. PET is not recommended for regular staging.

Management

Local therapy modalities are surgery and radiotherapy. For systemic therapy, conventional chemotherapy and increasingly also targeted therapies (i.e. interventions that affect tumor-specific structures at the molecular level)

are employed. Chemotherapy is polychemotherapy-so long as the patient's condition permits. Treatment for lung cancer is often multimodal. Radiotherapy and chemotherapy can be administered simultaneously as radiochemotherapy. Chemotherapy, radiotherapy, and radiochemotherapy may precede surgery (neoadjuvant therapy) or may follow it (adjuvant therapy). If a lung tumor with mixed histology contains a combination of small cell lung cancer and non-small cell lung cancer, it should be treated as small cell lung cancer.

Gastrointestinal Tract Cancer

About 85% of stomach cancers are adenocarcinomas with 15% due to lymphomas and gastrointestinal stromal tumors (GIST) and leiomyosarcomas. Gastric adeno carcinomas may be sub divided in to two categories; *a diffuse* type in which cell cohesion is absent, so that individual cells infiltrate and thicken the stomach, wall without forming a discrete mass and an intestinal type is characterized by cohesive *neoplastic cells* that form gland like tubular structures. Cancer is the leading cause of mortality in both developed and developing countries.

Annually, it causes around seven million deaths (about 13% of all causes of death) in the world and is the second most common cause of death in developed countries and among the top three causes of adult death in developing countries. Malignancies of the upper gastrointestinal (UGI) tract form a heterogeneous group of cancers characterized by uniqueepidemiology and biology. Also, esophageal cancer (EC) is among the 10 most common tumors and is the 6th leading cause of malignancy deaths worldwide. Smoking, alcohol consumption, Helicobacter pylori infection, dietary habits and obesity may be risk factors of gastric cancer. Most epidemiologic studies reported a risk of gastric cancer between 1.5 and 3.5 for subjects with relatives with gastriccancer.

Clinical Features

Gastric cancers, when superficial and surgically curable, usually produce no symptoms.

As the tumor become more extensive, patients may complain of an insidious upper abdominal discomfort varying in intensity from a vague, post prandial fullness to a severe, steady pain, anorexia often with slight nausea is very common but is not the usual presenting complaint. Weight loss, vomiting with nausea, dysphasia and early satiety may be the major symptoms caused by diffuse lesions originating in thecardia.

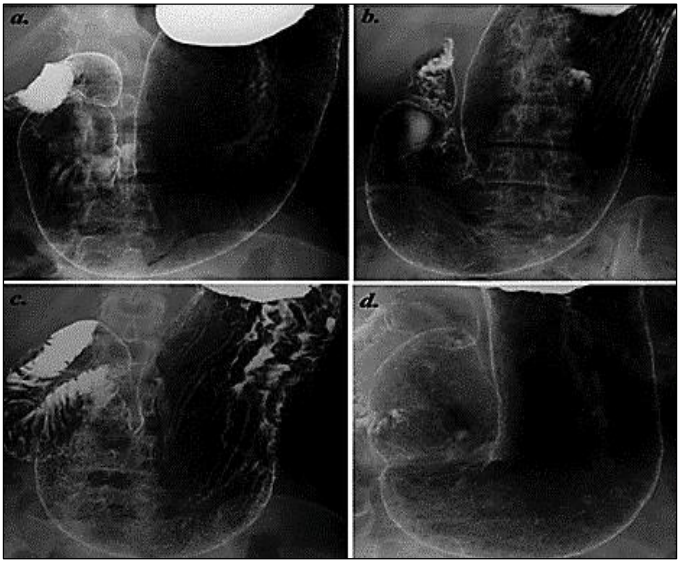


Fig 4: Contrast radiographic of GIT

Gastric carcinomas spread by direct extension through the gastric wall to the perigastric tissues, occasionally adhering to adjacent organs such as the pancreas, colon or liver. The disease also spreads via lymphatics or by seeding of peritoneal surfaces. Metastases to intra-abdominal and supra clavicular lymph nodes occur frequently as do metastatic nodules to the ovary (krukenbergs tumor), Perio umbilical region or peritoneal Cul de sac (blumers shelf palpable on rectal or vaginal examination). Malignant ascites may also develop. The liver is the most common site for hematogenous spread of tumor.

The presence of iron deficiency anaemia in men and of occult blood in the stool in both sexes mandates a search for an occult gastro intestinal tract lesion.

Diagnosis

Double contrast radiographic examination is the simplest diagnostic procedure for the evaluation of a patient with epigastric complaints. Gastric ulcer that appear benign by radiography present special problems. If complete healing can be visualized by x ray within 6 weeks and if a follow up contrast radiograph obtained several months later shows a normal appearance.

Management

Completes surgical removal of the tumor with resection of adjacent lymph nodes offers the only chance for cure. A subtotal gastrectomy is treatment of choice for patient with distal carcinomas, while total or near total gastrectomies are required for more proximaltumours.

Prostate Cancer

Benign and malignant changes in the prostate increase with age. Autopsies of men in eighth decade of life show hyperplastic changes in more than 90% and malignant changes in more than70% of individuals.

Aetiology

The relative risk of developing prostate cancer is higher (RR = 2.48; 95% CI 2.25-2.74) in men who have a first-degree relative with prostate cancer.

This risk is higher in men under 65 (RR = 2.87; 95% CI 2.21-3.74) compared to older men, and if the affected relative was a brother rather Thana father (RR = 3.14; 95% CI 2.37-4.15). Family history is clearly important, but only 35% of the familial risk is currently explained by known genes. Although rare (about 1 per 300), a BRCA2 mutation confers up to an 8.6-fold increased risk in men below 65 years of age, and such mutations have also been related with aggressive cancer. Some studies, but not all, havesuggested that the risk for prostate cancer is increased in men with a history of urinary tract infections. Infectionsmight influence the risk for prostate cancer by causing chronic intra-prostatic inflammation, and pathological studies have also suggested that inflammation may be involved in the development of prostate cancer. Smoking is associated with a moderate increase in the risk of prostate cancer. This association is much stronger and the increase more pronounced for aggressive or fatal cancers, particularly in current or heavy smokers who appear to be at a 2-fold or higher risk. For sex hormones, a pooled analysis of individual participant data from 18 studies found no significant associations but more data are needed to explore the relationship where both, decreased overall risk and an increased risk of high- grade cancer have been reported. Or insulin-like growth factors (IGFs), a pooled analysis of individual participant data from 12 studies showed a significant positive association between circulating IGF-I and prostate cancer risk more data are required on IGF-II and IGF bindingproteins.

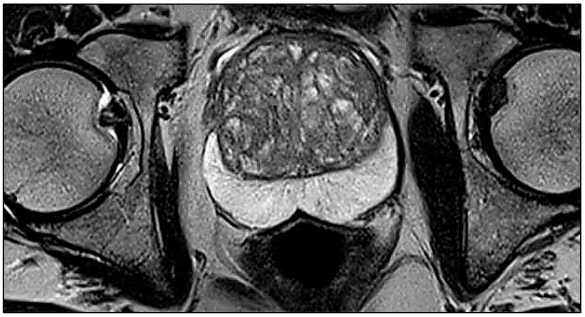


Fig 5: MRI of the Prostate cancer

Clinical Features

Most prostate cancer diagnoses are made in symptomatic men. Prostate cancer should be suspected in men over 50 years old presenting with lower urinary tract symptoms (LUTS), visible haematuria or erectile dysfunction. LUTS are also a common presenting symptom of benign conditions affecting the prostate, such as benign prostatic hyperplasia (BPH) and prostatitis, creating a diagnostic challenge. The widespread use of PSA as a screening test for prostate cancer in some countries has led to increasing diagnoses being made in asymptomatic men. Men may present to their doctor complaining of LUTS or other genitourinary symptoms, and are thus investigated for prostate cancer. It also is suspected that there are a significant number of men who go through life and die with undiagnosed prostate cancer; this suspicion is based on the findings of autopsy studies showing that up to three quarters of men over the age of 85 had neoplastic changes in the prostate, not all of whom had been diagnosed prior to their death.

LUTS are very common as men get older, with studies estimating a prevalence of greater than 50% in men aged 50 years and above, increasing further with increasing age. Other genitor urinary symptoms may also suggest that an undiagnosed prostate cancer is present. Visible haematuria is well established as a high-risk symptom for possible urological cancer, including prostatecancer.

Diagnosis

Debate continues around the role of PSA in the early detection and diagnosis of prostate cancer. PSA levels can be raised by a number of benign conditions, including BPH, prostatitis, ejaculation, and exercise (false positive). PSA can be within the normal range for up to 25% of men with prostate cancer (false negative). Urine dipstick testing, with or without

microscopy, culture and sensitivities (MC&S) should be performed prior to PSA testing to rule out lower urinary tract infection. The current gold standard diagnostic test for prostate cancer is a prostate biopsy, usually via a transrectal (TRUS) or transperineal approach guided by ultrasound. Primary care clinicians suspecting prostate cancer after assessing a patient or finding an elevated PSA result should refer on a cancer pathway to their local urological service for diagnostic testing.

Management

Localized prostate cancers are those that appear to be non-metastatic after staging studies are performed. Patients with localized disease are managed by radical surgery, radiation therapy or active surveillance. Choice of therapy requires the consideration of several factors: the presence of symptoms, the probability that the untreated tumor will adversely affect the patient during his life time and thus require treatment and the probability that the tumor can be cured by single modality therapy directed at the prostate or requires both local and systemic therapy to achieve cure. As most of the tumors detected are deemed clinical significant most men undergo treatment. Radical prostatectomy is to excise the cancer completely with a clear margin to maintain continence by preserving the external sphincter and to preserve potency by preserving the autonomic nerve in the neurovascular bundle. Radiation therapy is given by external beam by radioactive sources implant in to the gland or by acombination.

Chapter - 10

Diabetes Mellitus

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of diabetes mellitus are caused by a complex interaction of genetics and environmental factors depending on the etiology of diabetes mellitus.

Factors contributing to the hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production. The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, diabetes mellitus is the leading cause of end stage renal disease, non-traumatic lower extremity amputations and adult blindness. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide diabetes mellitus willbe the leading cause of morbidity and mortality for the seeablefuture.

Classification of Diabetes Mellitus

Diabetes mellitus classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as onset or type of therapy. The two broad categories of diabetes mellitus are designated type 1 and type 2. Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progress. Type 1 diabetes mellitus is the result of complete or near total insulin deficiency. Type 2 diabetes mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production.Distinct genetic and metabolic defects in insulin action and secretion give rise to the common phenotype of hyperglycemia in type 2 diabetes mellitus and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 diabetes mellitus is preceded by a period of abnormal glucose homoeostasis classified as impaired fasting glucose or impaired glucose tolerance.

Two features of the current classification of diabetes mellitus diverge from previous classifications. First, the terms insulin dependent diabetes mellitus [IDDM] and non-insulin dependent diabetes mellitus [NIDDM] are obsolete. Since many individuals with type 2 diabetes mellitus eventually require insulin treatment for control of glycaemia. The use of the term NIDDM generally considerable confusion. A second difference is that age is not a criterion in the classification system. Although type 2 diabetes mellitus most commonly develops before the 30, an auto immune beta cell destructive process can develop at any age. It is estimated that between 5 and 10 % individuals who develop diabetes mellitus after age of 30 years have type 1 diabetes mellitus. Although type 2 diabetes mellitus more typically develops with increasing age, it is now being diagnosed more frequently in children and young adults, particularly in obese adolescents.

Other Types of Diabetes Mellitus

Other etiologies for diabetes mellitus include specific genetic defects in insulin secretion or action, metabolic abnormalities that impair insulin secretion, mitochondrial abnormalities and a host of conditions that impair glucose tolerance. Maturity onset diabetes of the young [MODY] is a subtype of diabetes mellitus characterized by autosomal dominant inheritance, early onset hyperglycemia [usually < 25 years] and impairment in insulin secretion. Mutations in the insulin receptor cause a group of rare disorders characterized by severe insulinresistance.

Diabetes mellitus can result from pancreatic exocrine disease when the majority of pancreatic islets are destroyed. Cystic fibrosis related diabetes mellitus is an important consideration in the patient population

.Hormones that antagonize insulin action can also lead to diabetes mellitus. Thus diabetes mellitus is often a feature of endocrinopathies such as acromegaly and Cushing's disease. Viral infections have been implicated in pancreatic islet destruction but are an extremely rare cause of diabetes mellitus. A form of cute onset of type 1 diabetes mellitus, termed fulminant diabetes, has been noted in Japan and may be related to viral infection ofislets.

Pathophysiology

Type 2 diabetes mellitus is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production and abnormal fat metabolism.

Obesity, particularly visceral or central [as evidenced by the hip- waist ratio], is very common in type 2 diabetes mellitus [80% or more are obese].

In the early stages of the disorder, glucose tolerance remains near normal, despite insulin resistance, because the pancreatic beta cell compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately beta cell failure census.

Clinical Features

Type 2 diabetes mellitus present with polyuria and polydipsia, but unlike type1 diabetes, patients are often older [over 40 years] and frequently obese. However, with the increase in obesity and sedentary life style in our society, type 2 diabetes is now seen in children and adolescent with increasing frequency. In some medical attention is sought because of unexplained weakness or weight loss. Most frequently, however, the diagnosis s made after routine blood or urine testing in asymptomatic persons. The infrequency of ketoacidosis and milder presentation in type 2 diabetes is presumably because of higher portal vein insulin levels in these patients than in type 1 diabetics, which prevents unrestricted hepatic fatty acid oxidation and keeps the formation of ketone bodies in check. In the decompensated state, these patients may develop hyperosmolar nonketotic coma due to severe dehydration resulting from sustained osmotic diuresis [particularly in patients who do not drink enough water to compensate for urinary losses from chronic hyperglycemia].

Typically, the patient is an elderly diabetic who is disabled by stroke or an infection and is unable to maintain adequate water intake. Furthermore, the absence of ketoacidosis and its symptoms [nausea, vomiting, respiratory difficulties] delays the seeking of medical attention until severe dehydration and coma occur.

Diagnosis

Urine Testing

Testing the urine for glucose is the usual procedure for detecting diabetes, using sensitive glucose specific dipstick methods. If possible, the test for urinary glucose should be performed on urine passed 1-2 hours after

a meal since this will detect more cases of diabetes than a fasting urine specimen. Glycosuria always warrants full assessment.

The greatest disadvantage of using urinary glucose as a diagnostic or screening procedure is the individual variation in renal threshold. Thus some undoubtedly diabetes individuals will have a negative urine test while other non-diabetic individuals with a low renal threshold for glucose concentration, using an accurate laboratory method rather than a side room technique, is therefore essential in making the diagnosis. Ketone bodies can be identified by the nitroprusside reaction, which is primarily specific for acetoacetate and is conveniently carried out using tablets or test papers. Ketonuria may be found in normal people who have fasting or exercising strenuously for long periods, who have been vomiting repeatedly, or who have been eating a diet high in fat and low in carbohydrate. Ketonuria is therefore not pathognomonic of diabetes but, if associated with glycosuria, the diagnosis of diabetes is practically certain.

Oral Glucose Tolerance Test (OGTT)

When random blood glucose values are elevated but are not diagnostic of diabetes, glucose tolerance is usually assessed by the glycemic response to oral ingestion of a glucose load. The diagnostic criteria for diabetes mellitus and normality recommended by the World Health Organization (WHO) in 1980 are shown in table 2. The values are based on the threshold for risk of developing vascular disease. Intermediate readings are classified as ‘impaired glucose tolerance ‘(IGT) and indicate the need for further evaluation. Many patients and indicate the need for further evaluation. Many patients with IGT progress to frank diabetes with time, and it may be necessary, therefore, to keep such patients under review and to repeat the OGTT at a later date.

Management

Various drugs are effective in reducing hyperglycemia in patients with type 2 diabetes mellitus. Although their mechanisms of action are different most depend up on a supply of endogenous insulin and they therefore have no hypoglycemia effect in patients with type 1 diabetes.

Low calorie and sugar free drinks are useful for patients with diabetes. As diabetes is a risk factor for macro vascular disease intake of fat should be restricted to less than 40% if energy with less than 10% as saturated fat.

Chapter - 11

Infectious Diseases

Yellow Fever

Yellow fever caused by a flavivirus. It is normally a zoonosis of monkeys that inhabit tropical rainforests in west and central Africa and south and Central America. It can be transmitted to humans through the bites of certain *Aedes*or *Haemagogus* species of mosquitoes and has distinct transmission cycles in the jungle (sylvatic cycle), in the African savannah (intermediate cycle), and in cities (urban cycle).

Pathology

In the liver acute mid zonal necrosis leads to deposits of hyaline called councilman bodies and intra nuclear eosinophilic inclusion called torres bodies, another characteristic features is the absence of inflammatory infiltrate. The kidneys show tubular degeneration, which may partly be due to reduced blood flow. Haemorrhage is due to liver damage and disseminated intravascular coagulation.

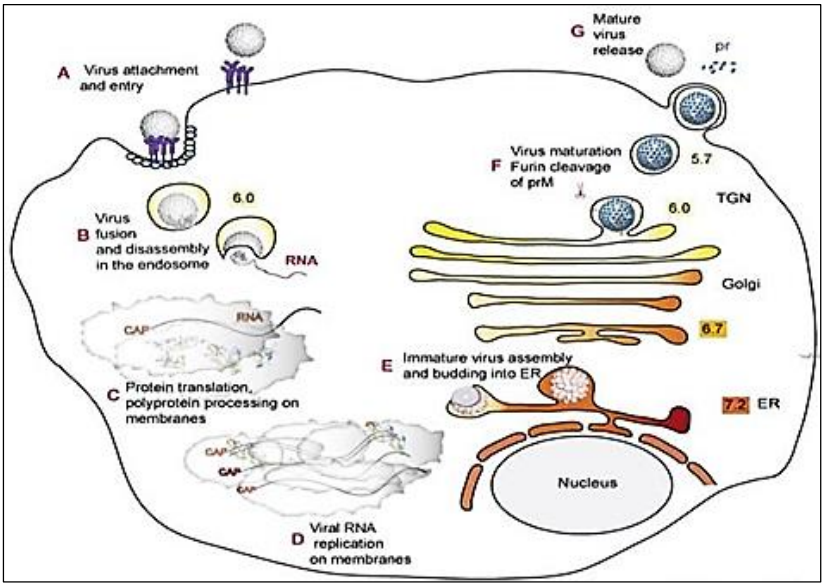


Fig 1: Flavivirus life cycle

Clinical Features

Clinically, many people infected with YFV are asymptomatic. Others develop symptoms including sudden fever, chills, headache, low back pain, myalgia, nausea, vomiting, and/orfatigue.

After an incubation period of approximately 3 to 6 days. Most with YFV disease improve within 3 to 4 days. However, roughly 15% go on to develop a more severe form of YFV disease with high fever, bleeding diatheses, abdominal pain, renal failure, cardiovascular instability, and/or liver failure and jaundice (hence the name "yellow fever"), and 20% to 50% of these patients may die. Additionally, neurologic complications may occur in those with YFV disease including headache, photophobia, agitation, seizures, encephalopathy, or rarely cerebral edema andcoma.

Diagnosis

Virus isolation from blood in first 4 days. Post mortem liver biopsy.

Management

Patients should be nursed under a mosquito net until the viraemic stage has passed. A single vaccination with the 17 D nonpathogenic strain of virus given full protection for at least 10years.

Dengue

This disease is the most common Flavivirus infection of humans and is a risk in May tropical and subtropical countries. The dengue virus, a member of the genus *Flavivirus* of the family Flaviviridae, is an arthropoda-borne virus that includes four different serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Two and a half billion people reside in dengue-endemic regions and roughly 400 million infections occurring per year, with a mortality rate surpassing 5-20% in some areas. The first reported case of dengue like illness in India was in Madras in 1780, the first virologically proved epidemic of DF in India occurred in Calcutta and Eastern Coast of India in 1963-1964. Dengue virus infection presents with a diverse clinical picture that ranges from asymptomatic illness to DF to the severe illness of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS).

Etiopathogenesis

DF is a severe flu-like infection that involves individuals of all age groups (infants, children, adolescents, and adults). Transmission among human beings occurs by the mosquito *Aedes aegypti* and chiefly occurs during the rainy season.

The proposed etiologies for dengue virus infection are:

- Viral replication, primarily inmacrophages
- Direct skin infection by thevirus
- Immunological and chemical-mediated mechanism induced by host–viralinteraction

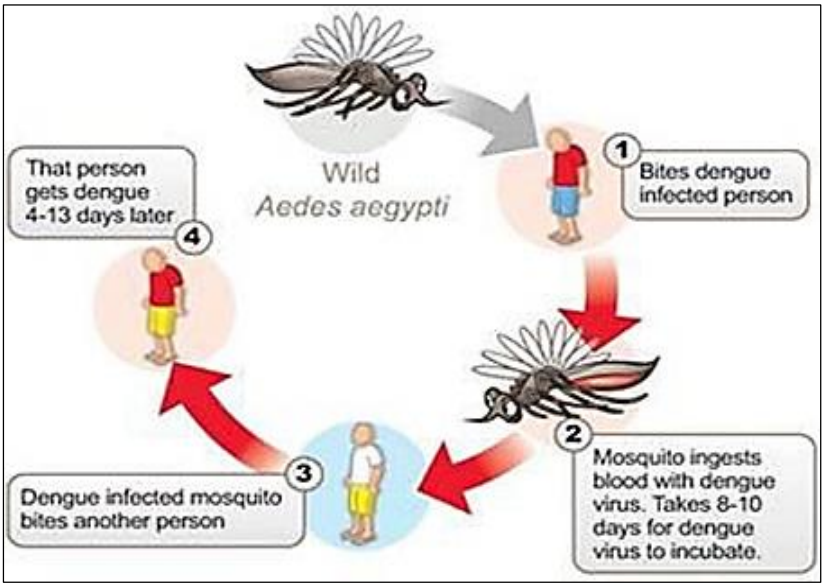


Fig 2: Dengue virus

Classification

Grade I: Only mild bruising or a positive tourniquet test.

Grade II: Spontaneous bleeding into the skin and elsewhere.

Grade III: Clinical sign of shock.

Grade IV: Severe shock-feeble pulse, and blood pressure cannot be recorded.

Here, grades III and IV comprise DSS.

Clinical Features

Prodrome are 2 days malaise and headache. Sudden onset of fever, backache, arthrlgias, headache, generalized pains (break bone fever), pain on eye movement, lacrimation, anorexia, nausea, vomiting, relative bradycardia, prostration, depression, lymphadenopathy, backache, arthrlgias, headache, generalized pains (break bone fever), pain on eye movement, lacrimation,

anorexia, nausea, vomiting, relative bradycardia, prostration, depression, lymphadenopathy, sclera injection. Fever continuous or saddle back with break on fourth or fifth day, usually lasts 7 to days. Rash are occurred transient macular in first 1-2 days. Maculopapular, scarlet morbilliform from days 3-5 on trunk, spreading centrifugally sparing palms and sole. May desquamate on resolution. DHF (Dengue hemorrhagic fever) is frequently seen during a secondary dengue infection. However, in infants it may also occur durring a primary infection due to maternally attained dengue antibodies. Clinical parameters: Acute-onset febrile phase-high-grade fever lasting from 2 days to 1 week. Hemorrhagic episodes (at least one of the following forms): Petechiae, purpura, ecchymosis, epistaxis, gingival and mucosal bleeding, GIT or injection site, hematemesis and/or malena. Laboratory parameters: Thrombocytopenia (platelet count <100,000/cu mm). The hemorrhagic episodes in DHF are associated with multifactorial pathogenesis. Vasculopathy, deficiency and dysfunction of platelets and defects in the blood coagulation pathways are the attributed factors. Decreased production of platelets and increased destruction of platelets may result in thrombocytopenia in DHF. The impaired platelet function causes the blood vessels to become fragile and this results in hemorrhage. High plasma escape cases are marked by frank shock with low pulse pressure, cyanosis, hepatomegaly, pleural and pericardial effusions, and ascites. Severe ecchymosis and gastrointestinal bleeding followed by epistaxis may also be noted in a few cases. Bradycardia, confluent petechial rashes, erythema, and pallor are seen during this phase.

Investigations

Cautious attention should be directed at DF if a patient suffers from high fever within 2 weeks of being in the tropics or subtropics.

A decreased number of white blood cells (leukopenia), accompanied by a decreased number of platelet count (thrombocytopenia) and metabolic acidosis are the initial changes on laboratory examinations. Microbiological laboratory testing confirms the diagnosis of DF. Virus segregation in cell cultures, nucleic acid demonstration by polymerase chain reaction (PCR), and serological detection of viral antigens (such as NS1) or particular antibodies are the preferred microbiological assays. Viral segregation and nucleic acid demonstration provide precise diagnosis, although the high cost limits the availability of thesetests.

Management

There is no specific treatment. Fluid replacement and antipyretic therapywith paracetamol is the preferred therapy following the febrile phase.

Care should be taken not to use other non-steroidalanti-inflammatory drugs. Oral lesions are infrequently seen and are often misguided as platelet defects. Significant hemorrhagic manifestations need platelet transfusions.

Mumps

Mumps is spread by droplet infection and affects mainly children of school age and young adults. The infectivity rate is not high and there is serological evidence that 30-40% of infections are clinically unapparent.

Clinical Features

Malaise, fever, trismus, pain near the angle of the jaw, swelling of one or both parotid gland. The sub Mandibular salivary glands may also be involved.

Investigation

Different diagnosis is from salivary calculus, which is unilateral, and sarcoidosis which cause bilateral chronic parotitis.

Management

Mumps vaccine is given in two dose with measles and rubella vaccines shortly after the first birthday and prior to school entry for prevention.

Enteric Fever

Typhoid and paratyphoid fever in many countries where sanitation o primitive.*Salmonella enterica*subspecies *enterica* serovar Typhi (*Salmonella* Typhi) is the cause of typhoid fever and a human host-restricted organism. Our understanding of the global burden of typhoid fever has improved in recent decades, with both an increase in the number and geographic representation of high-quality typhoid fever incidence studies, and greater sophistication of modeling approaches.

The 2017 World Health Organization Strategic Advisory Group of Experts on Immunization recommendation for the introduction of typhoid conjugate vaccines for infants and children aged >6 months in typhoid-endemic countries is likely to require further improvements in our understanding of typhoid burden at the global and nationallevels.

Causes

The enteric fever are caused by infection with salmonella typhi and salmonella paratyphi A and B. Humans are the reservoir (defined as the habitat in which the agent normally lives, grows, and multiplies) of *Salmonella* Typhi. *Salmonella* Typhi has limited capacity to multiply outside

of the human host, but it may survive for extended periods in the environment.

Pathology

The mode of *Salmonella* Typhi transmission is considered to be largely indirect and predominantly vehicle-borne through contaminated water or food. Water and food usually serve as passive vehicles for *Salmonella* Typhi. While *Salmonella* Typhi may survive for extended periods on vehicles, multiplication of *Salmonella* Typhi in water and food is uncommon. Some group *Salmonella* Typhi transmission into 2 broad patterns. In short-cycle transmission, food and water are contaminated by fecal shedding in the immediate environment, and transmission is mediated through inadequate hygiene and sanitation measures. In long-cycle transmission there is contamination of the broader environment, such as pollution of untreated water supplies by human feces and use of raw human feces or untreated sewage as a crop fertilizer.

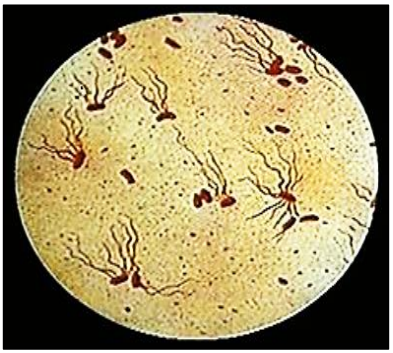


Fig 3: Typhoid fever

Clinical Features

First week symptoms are fever, headache, myalgia, bradycardia, constipation (diarrhoea and vomiting). End of the first week is rose spots on trunk, splenomegaly, cough, abdominal distension and diarrhoea. End of the second week is delirium, complications, then coma and death.

Investigations

Although there is a decline in the incidence of *S.* Typhi, the true isolation of *S.* Typhi from blood cultures is still challenging. Diagnosis of typhoid fever by conventional blood culture is challenging and time consuming as it takes about 24-48 h, after which the culture bottle flags positive. Although it is the gold standard method for detection of *S.* Typhi in

the blood, turnaround time plays a significant role in the management. WIDAL slide agglutination test is the second most commonly prescribed test. Yet, poor sensitivity and specificity is a limitation. Due to this, commercial rapid diagnostic tests (RDTs) are of great interest. However, owing to the poor sensitivity and specificity rates, definite detection is still limited. Typhidot-M, TUBEX-TM and Test-it are the three serological-based tests that have been evaluated. Performance of these tests have been shown to be poor and variable due to the high rates of disease burden in Asia, which is endemic for typhoid. In contrast, evaluation done in the Philippines has shown high sensitivity and specificityrates.

Complication

Complication of the enteric fever is perforation and haemorrhage of bowel, bone and joint infection, meningitis, cholecystitis, myocarditis, nephritis.

Management

Several antibiotics are effective in enteric fever.

Prevention

Those who propose to travel to or live in countries where enteric infections are endemic should be inoculated with one of the three available typhoid vaccines two inactivated inject able and one oral live attenuated).

Malaria

Human malaria is caused by plasmodium falciparum, plasmodium vivax, plasmodium ovale and plasmodium malariae. Malaria is a parasitic infection transmitted by mosquitoes that has afflicted humans over the millennia. Once endemic in the United States and Canada, it is now confined to more tropical and subtropical climates, particularly Africa. Despite advances in knowledge, malaria continues to cause significant morbidity and mortality worldwide. Malaria is one of the most prevalent human infections worldwide. Over 40% of the world's population live in malaria-endemic areas.

Exact numbers are unknown, but an estimated 300 to 500 million cases and 1.5 to 2.7 million deaths occur each year [3]. Ninety percent of deaths occur in sub-Saharan Africa, the majority involving children less than 5 years of age. Malaria disproportionately affects the poor, in whom higher morbidity and mortality can be largely attributed to lack of access to effective treatment; 60% of malaria deaths worldwide occur in the poorest 20% of the population.

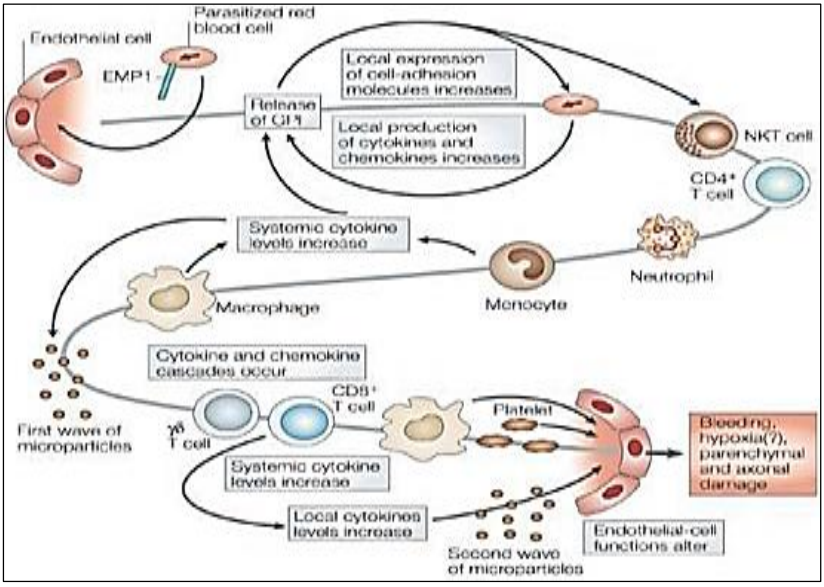


Fig 4: Malaria

Plasmodia species are the parasites responsible for malaria. Only 4 of the over 100 species of plasmodia are infectious to humans. The parasite is transmitted by night biting *Anopheles* mosquitoes. High parasite burdens combined with the unique ability of infected erythrocytes to adhere to host endothelium contribute to microvascular occlusion, metabolic derangement and acidosis, which lead to the manifestations of severe malaria (acute respiratory distress syndrome, renal insufficiency and cerebralmalaria).

In addition, a vigorous cytokine response to parasite proteins released during schizont rupture can contribute to adverse clinical outcomes.

Clinical Features

Fever, headache, a feeling of cold and arthralgias are common presenting symptoms in children. Anemia, splenomegaly and hepatomegaly are commonly associated with malaria.

Complications

- Organ damage due to anoxia are brain is confusion,coma
- **Kidney:** oliguria, uraemia (acute tubular necrosis)
- **Lung:** Cough pulmonaryoedema
- **Intestine:** Diarrhoea, congestion, possibly leaky tobacteria

- **Liver:** Jaundice, encephalopathy (rare)
- Hypoglycemia, shock secondary to septicaemia, hypotension shock, metabolic acidosis, splenic rupture

Investigations

Hematologic abnormalities are common: thrombocytopenia (platelet count < 150 x 10^9/L) occurs in up to 70% of patients and anemia in 25%. The leukocyte count is normal or low; leukocytosis is seen in less than 5% of cases and is a poor prognostic factor. A high degree of suspicion and rapid diagnosis are essential to optimize outcome. Thick and thin peripheral blood smears, stained with Giemsa stain (or, alternatively, Wright's or Field's stains), remain the "gold standard" for routine clinical diagnosis. Rapid antigen detection tests (RDT) RDTs currently available can identify only *P. falciparum* and *P. vivax*, however. Malaria rapid test, manufactured by Makro Medical (Pty) Ltd., is the only test currently licensed for use in Canada. Important shortcomings of RDTs include their inability to quantitate parasitemia and suboptimal test performance with low-level parasitemia. Further more, because antigenemia may persist for prolonged periods even after treatment.

Management

The treatment of malaria depends on the infecting plasmodia species, the geographic area of acquisition (which affects the likelihood of drug resistance) and the severity of infection. Falciparum malaria in the nonimmune person is a medical emergency and requires rapid initiation of antimalarial therapy. If the species cannot be immediately identified, the patient should be assumed to have drug-resistant falciparum malaria until proven otherwise. Hospital admission is advised for those with falciparum malaria or in whom the infecting species cannot be identified, and for those who are severely ill.

Chapter - 12

Diseases of the Blood

Anemia

Diminished oxygen carrying capacity of the blood.

Causes: Decreased or ineffective marrow production like lack of iron, B12 or folate, hypoplasia, invasion by malignant cells and peripheral causes are blood loss, haemolysis, hypersplenism.

Clinical Features

Symptoms of anaemia are lassitude, breathlessness on exertion, fatigue, palpitations, throbbing in head and ears, dizziness, tinnitus, headache, diminish of vision, insomnia, paraesthesia in fingers and toes, angina. Signs are pallor of skin, mucous membranes, palms of hands, conjunctive, tachycardia, cardiac dilation, systolic flow murmurs, oedema.

Diagnosis

Complete blood picture (Hb%) can be find out anaemia.

Iron Deficiency Anaemia

Iron deficiency usually results from loss of iron because of bleeding and inadequate diet or malabsorption. Occasionally, iron may be lost in the urine in the form of hemosiderin.

Causes: Iron deficiency is gastrointestinal bleeding-example, from gastric erosions associated with anti-inflammatory drugs, neoplastic disease and peptic ulcers. Hook worm and schistosoma is also very common in iron deficiency anaemia, diet containing inadequate iron can cause or contribute to iron deficiency anemia.

Clinical Features

Nausea, vomiting, weakness, dyspnoea, numbness, pallor, cardiomegaly splenomegaly.

Diagnosis

The haematological findings are a reduced haemoglobin with normal or slightly reduced red cell count and a low mean cell volume of less than 76 fl.

Raised platelet count may suggested that bleeding is the cause of the deficiency.

Management

Most patient can be treated orally and ferrous sulphate given as a tablet containing 200 mg of the salt 8^{th} hourly.

Megaloblastic Anaemia

This condition is caused by deficiency of vitamin B_{12} and folic acid. Deficiency of either or both cause a failure of DNA synthesis and disordered cell proliferation.

Causes

Nutritional deficiency, chronic alcoholism, pernicious anaemia, carcinoma of stomach malabsorption syndrome, crohn's disease, congenital deficiency without gastric atrophy (rare), gastrectomy, pregnancy and lactation.

Clinical Features

Progressive weakness, occasional angina pain, palpitation, numbness, tingling in extremities, vomiting, diarrhoea. Signs are pallor, smooth tongue, optic atrophy, soft systolic murmur at apex, splenomegaly cardiomegaly, DTR's diminished.

Diagnosis

Haemoglobin, platelet count and RBC count level is low, peripheral smear is anisocytosis, poikilocytosis megalocytosis, polychromasia, punctate basophilia, leucopenia and elevated ESR.

Management

Vitamin B12 therapy (inj. Vitamin AB12 1000 mcg IM one injection on alternated days for total five injection, then once a week for 5 weeks, than once in 3 to 6 months will be adequate for most patients.

Pernicious Anaemia

It is due to a failure of secretion of intrinsic factor by the stomach other than from total gastrectomy. It is an autoimmune disease andin about 50% of patient's antibodies to intrinsic factor can be demonstrated. This disease is rare before the age of 30, occur mostly between 45 to 65 years, and more females compared to males. Hypovitaminosis B12 is common in adults and in elderly patients with a prevalence ranging from 15%-40% according to the various studies and definition used. It is often under diagnosed because of

subtle or polymorphous clinical manifestations. Its main etiology is represented by classic pernicious anemia (PA), also known as Biermer's disease. PA is an autoimmune atrophic gastritis that causes a deficiency in vitamin B12 due to its malabsorption. It accounts for 20%-50% of the documented causes of vitamin B12 (cobalamin) deficiency in adults according to a recentseries.

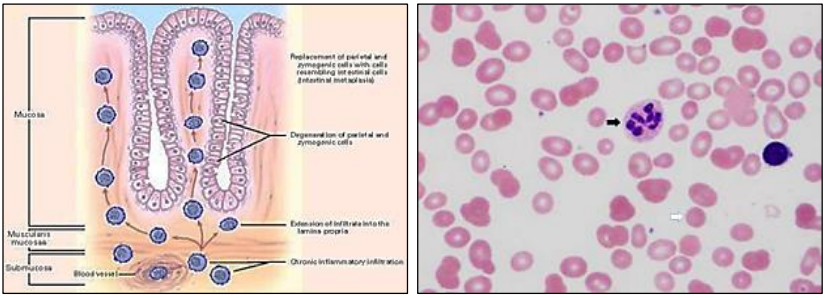


Fig 1: Pernicious anemia

Pathology

Increased blood destruction, including unconjugated hyperbilirubinemia and increased deposition of iron (hemosiderin) in the liver, spleen, kidneys and bone morrow. The gastric mucosa is thin and atrophic.

Clinical Features

Anemia is the most frequently encountered clinical sign during PA, together with accompanying functional manifestations, depending on their severity. It can often include a hemolytic component with subicterus. Hematological manifestations have also been commonly reported: neutropenia, thrombocytopenia, pancytopenia, intramedullary hemolytic component due to ineffective erythropoiesis, and pseudo thrombotic microangiopathy.

He most frequent signs are the presence of macroovalocytes and hypersegmented neutrophils on peripheral blood smears.

Diagnosis

Very low serum vitamin B12, often less than 50 ng/l, anti-intrinsic factor antibodies in serum (present in 50%), macrocytic dysplastic blood picture, megaloblastic marrow, abnormal vitamin B12 absorption test corrected by addition of intrinsic factor.

Management

It should be seriously considered when the haemoglobin level is so low as to endanger life-for example, under 49 g./. Hydroxocobalamin is given parenterally in a dosage of 1000 µg. After an initial dose injections are given every 2 to 3 days for a future five dose. Maintenance therapy consists of 1000 µg parenterally every three months.

Haemolytic Anaemia

Various abnormalities may shorten the normal red cell life span of 120 days. Anaemia develops when marrow output no longer compensates. The increased output of new erythrocytes is reflected in a raised reticulocyte count, which given an indication of the severity of the process. Haemolytic anaemia is the clinical condition in which antibodies of immunoglobulin G (IgG) and/or immunoglobulin M (IgM) bind to red cell surface antigens and initiate red cell destruction via the complement system and the reticulo endothelial system. IHA is classified as either autoimmune, allow immune or drug induced based on the antigenic stimulus responsible for the immuneresponse.

Autoimmune Hemolytic Anemia (AIHA) is characterized by the production of auto antibodies directed against red blood cells (RBC). Usually these autoantibodies are directed against high incidence antigens. But, often they exhibit reactivity against allogenic red cells.

First described by Coombs *et al*. in 1945, the anti-human globulin test uses antibody to human globulin and *in vivo* coating of red cells with antibody or complement.

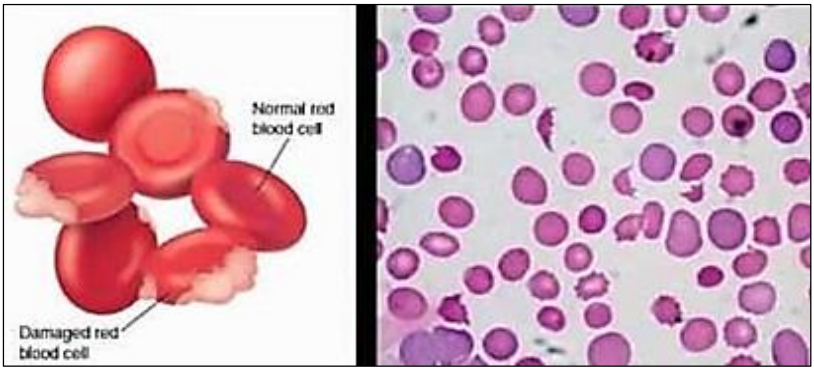


Fig 2: Haemolytic anaemia

Causes: Congenital are hereditary spherocytosis, hereditary elliptocytosis and lack of haemoglobin chain synthesis, thalassemias, amino

acid substitution on the haemoglobin chain haemoglobin S,C,D glucose-6-phosphate dehydrogenase deficiency, isoimmune (cold antibody, warm antibody), alloimmune, mechanical artificial cardiac valves, burns, infections. Warm autoantibodies react more strongly near 37 °C and exhibit decreased affinity at a lower temperature. Cold auto antibodies on the other hand, bind to red cells more strongly near 0-4 °C and generally show little affinity at physiologic temperature. Occasionally patients have a combination of warm and cold auto antibodies. It was observed by Petz and Garratty in 1980 and Sokol *et al*. in 1981 that warm auto antibodies are responsible for 48-70% of Haemolytic anaemia cases. Lymphoproliferative disorders such as chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma and Waldenstrom's macroglobulinemia are the leading causes of secondary cases. Cold-reactive auto antibodies cause two distinct clinical entities: CAS, (cold hemagglutinin disease) and paroxysmal cold hemoglobinuria (PCH). CAS represents approximately 16-32% of Haemolytic anaemiacases.

Clinical Features

Signs and symptoms may include fatigue, dizziness, heart palpitations, pale skin, headache, fever, confusion, lightheadedness, weakness or inability to do physical activity, dark urine, yellowing of the skin and the whites of the eyes (jaundice), heart murmur, increased heart rate and a spleen or liver that is larger thannormal.

Diagnosis

Bilirubin test measures the level of red blood cell haemoglobin that liver has broken down and processed. Haemoglobin test indirectly reflects the amount of red blood cells you have circulating in your blood (by measuring the oxygen carrying protein within your red blood cells). Liver function test is measures the levels of proteins, liver enzymes, and bilirubin in your blood. Reticulocyte count is measures how many immature red blood cells, which over time mature into red blood cells, that your body is producing. Bone marrow aspiration or biopsy test can provide information about how many red blood cells are being made and theirshape.

Management

Transfusion of red cells with a normal enzyme complement may be required. Thereafter, the patient should be advised to avoid drugs which may precipitate the disorder. Splenectomy is without value.

Sickle Cell Anaemia

A hereditary disorder characterized by abnormal haemoglobin in the RBC which makes them to assume a sickle shape at low oxygen tension.

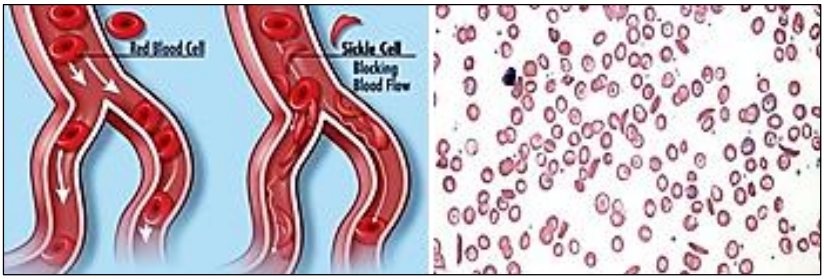


Fig 3: Sickle cell anaemia

Sickle cell disease (SCD) is the name for a group of genetic blood disorders caused by sickle hemoglobin (Hb S). The 2 key features of SCD are chronic hemolytic anemia and vaso occlusion. Although it is fundamentally a blood disease, SCD affects the entire body, and the pathophysiology begins in very early infancy. Pediatricians and family practitioners are crucial partners in the multidisciplinary team that is required to manage children with SCD. This book provides a broad overview of SCD in childhood, focusing on common complications and current treatments.

Causes

Inheritance: Autosomal dominant and effect both male, female.

Pathology

Hb is the oxygen-carrying protein in blood. It is a tetramer of 4 proteins, 2 α-globins and 2 β-globins. Each globin has an associated oxygen-binding heme group. The α-globins and β-globins are encoded by genes on different chromosomes. The Hb S mutation (β^S) is a single nucleotide substitution in the sixth codon of the β-globin gene (*HBB*). This yields a protein with a hydrophobic valine residue, instead of the normal hydrophilic glutamic acid at the sixth position that is prone to polymerization on deoxygenation. He polymerization of Hb S within red blood cells (RBCs) (“sickling”) on deoxygenation underlies all the pathophysiology of SCD. As Hb S-containing RBCs traverse the circulation undergoing cycles of oxygenation and deoxygenation, rigid polymers of Hb S repeatedly form and damage the RBC membrane, drastically shortening the RBC life span. RBCs also become dehydrated, relatively inflexible, and abnormally adhesive. Consequently, they are prone to adhere to the endothelium of blood vessels,

in concert with leukocytes and platelets, impeding the flow of blood. This microvascular obstruction, called vaso occlusion, leads to ischemia, infarction, and ischemia reperfusion injury of multiple organs and tissues. This pathophysiology produces an ongoing inflammatory response and endothelial dysfunction. Some complications of SCD can be considered to be primarily a consequence of either hemolysis or vaso occlusion.

For example, chronic hemolysis predisposes to bilirubinate cholelithiasis, whereas vaso occlusive ischemia and infarction of bone marrow is thought to cause the acute painful event ("crisis"), the hallmark of SCD. The pathophysiology of SCD is more complex than a simple "log jam" model of vaso occlusion by irreversibly sickled RBCs.

Clinical Features

Thrombosis follows and an area of tissue infarction results causing severe pain, swelling and tenderness (infarction crisis), weakness, leg ulceration, pallor, splenomegaly (moderate), biliary colic.

Diagnosis

Low haemoglobin, raised (20,000-50,000/cu mm), less than 1000, blast cells are 30%-90%, diminished platelet count, increased reticulocytes, normoblasts present, bone marrow preponderance of appropriate primitive cells.

Management

Preliminary experience with allogeneic transplantation has introduced the prospect of cure for the first time in the management of sickle cell patients, plenty of fluids, bed rest, maintain oral hygiene, well balanced, nutritious, easily digestiblediet.

Leukaemia

Abnormal proliferation of leukopoiesis tissues characterized by remarkable rise in blood leukocytes count, unexplained by reactive leukocytosis. It is considered to be multi factorial, including exogenous or endogenous exposures, genetic susceptibility, and chance. The survival rate of pediatrics leukaemia has improved to approximately 90% in recent trials with risk stratification by biologic features of leukaemic cells and response to therapy, therapy modification based on patient pharmacodynamics and pharmacogenomics, and improved supportive care. However, innovative approaches are needed to further improve survival while reducing adverse effects. An estimated 6000 new cases (3400 male and 2600 female) of acute lymphoblastic leukaemia (ALL) are diagnosed annually in the US. Patients are predominantly children.

Approximately 60% of cases occur at age <20 years. LL, like cancer in general, is likely to arise from interactions between exogenous or endogenous exposures, genetic (inherited) susceptibility.

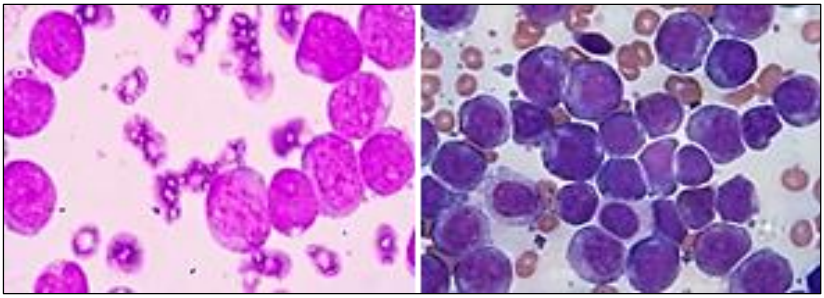


Fig 4: Leukaemia

Type: Acute leukaemia and chronic leukaemia.

Causes: Exact causes is not known. Neoplastic theory–resemble malignant neoplasm, infiltrate and destroy normal tissues and interfere with their normal activity.

Clinical Features

Fever, chill weight loss, weakness, fatigue, nausea, vomiting, anorexia, apin and aches all over, petechiae, bruises, bleeding from nose, gums, haematemesis, haematuria, sore throat, stomatitis. Signs are pallor severe, generalized lymphadenopathy, cutaneous haemorrhage, bleeding gums, stomatitis, rapid pulse, hepatosplenomegaly, soft systolic murmur at apex.

Diagnosis

Morphological identification of lymphoblasts by microscopy and immunophenotypic determination of lineage commitment and developmental stage by flow cytometry are essential for correct diagnosis of ALL. Chromosomal analysis still plays an important role in the initial cytogenetic work-up. RT-PCR, FISH/multiplex ligation dependent probe amplification, and flow cytometry are used to identify leukaemia specific translocations, submicroscopic chromosomal abnormalities, and cellular DNA content, respectively. After genome wide analysis becomes time and cost effective, it may replace many current diagnostic techniques.

Management

Treat with fresh blood transfusion, plenty of oral fluids, correct anemia, well balanced nutritional diet, adequate rest, maintain oral hygiene.

Aplastic Anaemia

Most acquired aplastic anemia (AA) is the result of immune-mediated destruction of hematopoietic stem cells causing pancytopenia and an empty bone marrow, which can be successfully treated with either immunosuppressive therapy (IST) or hematopoietic stem-cell transplantation (HSCT). For these patients, comparable long term survival is attainable with immunosuppressive treatment (IST) with anti-thymocyte globulin (ATG) and cyclosporine (CsA). Although several etiopathogenic triggers have been proposed in AA, the majority of cases are idiopathic, with a small percentage of cases occurring after an episodeof seronegativehepatitis.

Acquired AA is a rare disease; almost half of cases occur during the first three decades of life. The incidence in Western countries is two cases per million per year and about 2-3-fold higher in Asia. During the lastcentury, AA was attributed to an idiosyncratic reaction to drug or chemical exposure. The association of medical drug use to AA is of great importance, as it is devastating to patients and physicians and presents serious legal consequences and problems in pharmaceutical drug development.

Causes: Drugs are like cytotoxic drugs, idiosyncratic, antibiotics, anti-rheumatic agents, immunosuppressives, benzene toluene solvent abuse, radiations, viral hepatitis, pregnancy, paroxysmal nocturnal haemoglobinuria.

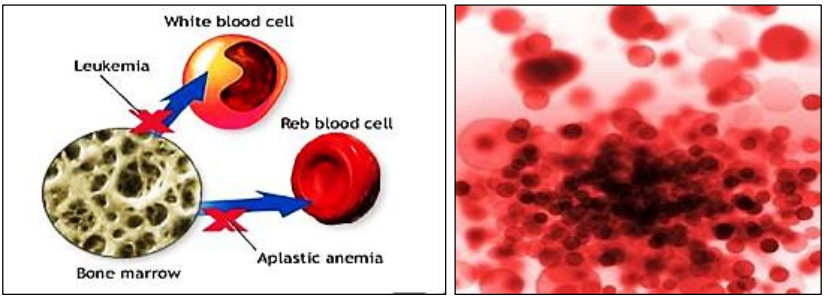


Fig 5: Aplastic Anemia

Pathology

In most cases, AA behaves as an immune-mediated disease. An immune response dominated by oligoclonal expanded cytotoxic T-cells targets hematopoietic stem and progenitor cells, inducing their death via apoptosis and hematopoietic failure. Recovery of autologous hematopoiesis in patients who failed to engraft after stem cell transplant and responsiveness to immunosuppressive therapies are the major clinical evidences supporting an

immune pathophysiology underlying acquired AA. Although a nonimmune pathophysiology has been inferred from a failure to respond to immunosuppression, refractoriness to therapy is also consistent with very severe stem cell depletion, a “spent” immune response, or immunological mechanisms resistant to currenttherapies.

Removal of lymphocytes from aplastic bone marrows improves colony numbers in tissue culture, and their addition to normal marrow inhibited hematopoiesis *in vitro*. The effector cells within the lymphocyte subset are activated cytotoxic T cells bearing a Th1 profile, expressing and secreting interferon-γ. T-bet, a transcription factor that binds to the interferon-γ promoter region and is critical for Th1 polarization, is up- regulated in T-cells of patients with AA. Specific CD8+CD28- cell clones are expanded in AA peripheral blood, as manifest by skewed usage of the Vβ repertoire; and oligoclonal recognize and induce apoptosis of autologous myeloid cells. Regulatory T cells, which control and suppress auto reactive T cells, are decreased at presentation in almost all patients with AA. In a mouse model of immune mediated marrow failure, addition of T regulatory cells abrogated pancytopenia induced by the infusion of lymph node cells. Why T-cells are activated in AA is unclear. HLA-DR2 is over represented among patients, suggesting a role for antigen recognition, and its presence is predictive of a better response to cyclosporine. Polymorphisms in cytokine genes, associated with an increased immune response, also are more prevalent, such as for tumor necrosis factor-α (*TNF2*) promoter at -308, interferon-γ, and interleukin 6 genes. These alterations in nucleotide sequence and in gene regulation suggest a genetic basis for aberrant T cell activation in bone marrow failure.

Clinical Features

Weakness, nausea, vomiting, weight loss, fatigue.

Diagnosis

A fatty bone marrow remains basic to diagnosis, but sophisticated testing now can be directed at distinguishing among diverse pathophysiologies and discriminating among similar, sometimes overlapping diseases why in the differential diagnosis.

Management

Replacement of a failed bone marrow is curative of the underlying disease. Transplant has been limited by its complications, graft rejection and graft-versus-host disease (GVHD), and the availability of suitable donors.

For immune aplastic anemia, transplant is always preferred in the young patient, and when undertaken expeditiously after diagnosis using his to compatible sibling donor, results are excellent, with more than 90% long term survival in young children.

More than 80% in adolescents, and a low rate of complications short and long term. Umbilical cord transplantation also has been successful in aplastic anemia, mainly in children due to the relationship between donor inoculum cell numbers and recipient weight, with survival approximating 90%. A potential donor half matched to the patient should be present in virtually every family. As even single antigen disparities markedly affect outcomes of transplants, overcoming major histocompatibility differences had seemed an insuperable barrier. T cell depleting strategies, pre transplant by cytotoxic drugs and biologics, and post-transplant with cyclophosphamide have been utilized to prevent GVHD.

Hodgkin's disease

Hodgkin lymphoma (HL) is a rare cancer that arises from immune cells known as B lymphocytes (B cells) and typically affects the lymph nodes and sometimes other organs or abnormal painless, progressive lymphoid proliferation with irregular fever, weight loss, excessive sweating having a chronic course marked by episodes of exacerbation and remissions. Hodgkin lymphoma (HL) is a rare cancer of the immune system that typically affects lymph nodes and sometimes other organs.

Although the majority of patients can be potentially cured with the use of multi-agent chemotherapy and radiotherapy, a proportion of them will relapse or develop resistant disease for which treatment options are limited. In recent years, new agents have been developed and tested in HL with encouraging results. The first descriptions of what came to be known as Hodgkin disease date back to 1832 when the eminent British pathologist Thomas Hodgkin described an autopsy case series of patients with lymphadenopathy and splenic enlargement. It was not till the late 1990s that our understanding of the entity as a malignancy arising from germinal center or post germinal center B cells led to the term 'Hodgkin lymphoma' (HL) gaining favor. Characteristically, the cancer cells form a minority of the tumor and are surrounded by a reactive inflammatory milieu comprising lymphocytes, eosinophils, neutrophils, histiocytes and plasma cells. These malignant cells can be pathognomonic multinucleate giant cells or large mononuclear cells and are together referred to as Hodgkin and Reed Sternberg (HRS) cells.

Causes: Exact causes unknown, history of infections mononucleosis.

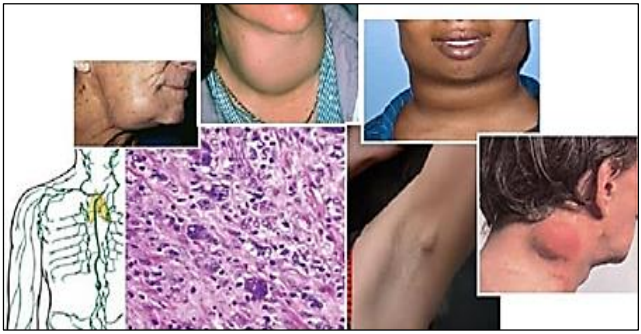


Fig 6: Hodgkin's disease

Clinical Features

Cervical lymph nodes enlargement with painless, unilateral, chest pain, cough, dyspnoea, dysphagia, hoarseness, fever irregular with sweat, alternating pyrexia and apyrexia, associated with enlarged mediastinal and abdominal lymph nodes, pruritus, anorexia, weight loss, sweating. Signs are mid anaemia, pallor, slight temperature; lymph nodes are moderately enlarged, discrete, rubbery, non-tender, splenomegaly, hepatomegaly.

Stages:

Stage 1: Single abnormal lymph node.

Stage 2: Involvement of lymph nodes (above diaphragm).

Stage 3: Involvement of lymph nodes (above and below diaphragm).

Stage 4: Extra lymphatic involvement.

Diagnosis

Low HB%, raised TLC, eosinophils raised in 15%, raised ESR.

Management

Well balanced diet. In determining the optimal treatment for patients with Hodgkin lymphoma, the factors that play a major role include the histologic features of the disease (classical Hodgkin lymphoma compared with nodular lymphocyte predominant Hodgkin lymphoma). The stage of the disease (particularly whether the patient has early or advanced stage disease), the presence of clinical factors that suggest a poor prognosis, the presence of systemic symptoms, and the presence or absence of a bulky mass, defined as a single site of disease greater than 10 cm in diameter. Fludeoxyglucose (FDG) ePET also plays a key role in defining the initial treatment.

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