LECTURE NOTES
ON
APPROACH TO PAEDIATRIC PATIENT

Dr M R Ghuman

MBBS (Pb), MSc Med (Wits), FC Paed (SA)

2nd Review 2012

INDEX

SOURCE OF INFORMATION

1. Churchill's Pass Paediatrics 1st ed
2. Students Clinical Methods: M Ali 4th ed
3. Macleod's Clinical Examination 11th ed
4. Clinical Examination: NJ Tally et al 5th ed
5. Examination Paediatrics: Wayne Harris 3rd ed
6. Clinical Paediatrics for post graduate students 3rd ed
7. Bates Guide to Clinical Examination and History Taking 4th ed
8. Ziai Bedside Pediatrics: Diagnostic Evaluation of the Child 1st ed
9. Parks Paediatric Cardiology for Practitioners 5th ed
10. Clinical Electrocardiography: MJ Goldman 12th ed
11. ECG Made Easy: JR Hampton 5th ed
12. Robbins Basic Pathology 8th ed
13. Practical Endocrinology and Diabetes in Children 2nd ed
14. Nelson Text book of Paediatrics 18th ed
15. Weiner and Levitt's Pediatric Neurology 4th ed
16. Nelson Essentials of Pediatrics 5th ed
17. Coovadia's Paediatrics and Child Health 6th ed
18. Child Health for All: Kibble, Saloojee, Westwood 4th ed
19. Concise Pathology: Chandrasoma et al 3rd ed
20. Handbook of Paediatrics: Motala et al 7th ed
21. Paediatric Guidelines: Mc Karrow, Patrick & Stephen et al
22. Forfar & Neil's Text Book of Paeditarics 18th ed
23. Neonatal Guidelines and Drug Doses: Alan Horn et al 2nd ed
24. Manual of Neonatal Care: Cloherty et al 6th ed
25. Drug Doses: Frank Shann13th ed
26. Classification of Drugs: M R Ghuman 1st ed
27. Katzung Basic Pharmacology 10th ed
28. Pharmacology: Howlands et al 3rd ed
29. General Pharmacology: M R Ghuman 1st ed
30. Basic epidemiology: Beaglehole et al
31. Basic & Clinical Biostatics: Dawson et al 3rd ed
32. Langman's Medical Embryology 10th ed
33. Ganong Review of Medical Physiology 22nd ed
34. South African Family Practice Manual: Bob Mash et al 2nd ed
35. Journal Articles: Lancet, BMJ, SAMJ, SAJCN, Paeditaric Quarterly etc.
36. Problem Rounds & Clinical Meetings 2008 to 2011 @ UKZN
37. PICU Grand Rounds & Mock FCP tutorials 2008 to 2011 @ UKZN

PULMONOLOGY

CHILD WITH CHRONIC LUNG DISEASE

HOST PROBLEMS

Congenital/hereditary

1. Anomalies of the lung:
   - Cysts
   - Sequestration
2. Congenital lobar emphysema
3. Mucociliary clearance dysfunction:
   - Cystic fibrosis
   - Immotile cilia syndrome
   - Mucocilliary dyskinesia
   - Ectodermal dysplasia
4. Alpha 1 antitrypsin deficiency
5. Primary Immunodeficiency Disorders:
   - Phagocytic function defects
   - B cell deficiency
   - T cell deficiency

Allergic/hypersensitivity

1. Asthma
2. Allergic bronchopulmonary aspergillosis
3. Hypersensitivity pneumonitis (drugs/chemicals)
4. Heiners syndrome (cow's milk hyper-reactivity)

Mechanical/anatomical obstruction

1. Intraluminal FB
2. Extraluminal FB e.g. regional lymph nodes
3. Bronchial stenosis

Respiration disorders

1. Abnormal swallowing reflex
2. CNS and musculo-skeletal disorders
3. Tracheo-oesophageal fistula i.e. H-type
4. Gastro-oesophageal reflux disease

Systemic disease

1. Sarcoidosis
2. Wagners granulomatosis
3. Collagen diseases: Ehlers Danlos, Marfans syndrome
4. Malignancy
5. Reticuloendotheliosis
   - Gauchers dx
   - Niemann Pick dx
   - Histiocytosis

Idiopathic

1. Pulmonary haemosiderosis
2. BPD
3. Fibrosing alveolitis
4. LIP
5. Young syndrome: bronchiectasis + sinusitis + obstructive azoospermia but with normal cilliary function

ORGANISM PROBLEMS –INFECTIOUS CAUSES

A. Infections

1. Underlying HIV
2. Pesistant or recurrent infections
    - Clamydia
    - TB (diagnosis is based on chronicity of illness, matted LAD, upward curling of eye lashes and fundoscopy (nodules in vessels – granuloma formation)
    - Atypical mycobacterium
    - Histoplasmosis
    - CMV
    - Visceral larva migrans
    - Pneumocystis Jirovici

B. Post infectious

1. Bronchiectasis
2. Nectrosing Bronchiolitis obliterans
3. Interstitial fibrosis
4. IRIS

Chronic lung disease: Common causes: (Mock FCP, May 2011)

1. Chronic suppurative lung disease with bronchiectasis
2. Primary progressive TB
3. Cystic fibrosis
4. Alpha 1 antitrypsin deficiency
5. Tracheo-oesophageal fistula (H-type)
6. Mucociliary dyskinesis - only 40 % have situs inversus

Investigations for Chronic Lung Disease

1. Bloods
   - ABG
     - Hypoxia – interstitial disease
     - Hypercapnoea – airway disease
   - Inflammatory markers
     - FBC and diff
     - LDH
     - Globulin fraction
     - ESR
     - CRP
   - HIV: PCR / ELISA
     - CD4, viral load (response to ARVs)
2. Microbiological
   - Blood culture (Bectec)
   - Mantoux
   - Induced sputum
     - AFB
     - MCS
     - Fungal elements
     - Viral studies
     - PJP
3. More invasive sampling depends upon experties
   - Endotracheal aspirates
   - Bronchoscopy
   - BAL
   - Protective brush specimen
   - Close transbroncheal biopsy
   - Open lung biopsy
   - Pleurocentesis
   - Pleural biopsy
   - Lung aspiration – where consolidation (20 cc syring + 5 cc sterile water inject then aspirate (Dr Thula)
   - Lymph node biopsy
4. Miscellaneous
   - Serial CXR
   - High resolution CT chest: to identify which segment is involved & for operation purpose
   - Lung function tests
   - ECG / Echo (PHT, cor pulmonale, RVH)

SHORT NOTES

1. Transient hypogammaglobulinaemia

- It may occur between 18-24 months
- Child presents with recurrent diarrhea, otitis media, respiratory infections & wheezing
- Child may need treatment with gammaglobulin until endogeneous synthesis rates are normal

2. Isolated IgA deficiency

- The most common type of immunodeficiency encountered
- Selective IgA deficiency is increased in children with respiratory allergy & ataxia telangiectasia
- Some deficient children can substitute low mol. wt IgM for the deficient IgA & maintain immunological defences at mucosal surfaces of GI & sinopulmonary epithelium

3. Pulmonary sequestration (Nelson p1465)

- Loss of connection of lung tissue with the broncheal tree and the pulmonay veins. It is mass of embryonic tissue that does not communicate witH broncheal tree and does not participate in ga exchange. It has systemic arterial supply and associated CHD is common
- Abnormality on CXR: Triangular density at left lung base extending to mediastinum
- Repeated respiratory infections can be prevented by surgical removal

4. Cystic adenomatoid formation

Congenital cystic disease of lung

- Three types
  - Type I: Multiple large cysts 70%
  - Type II: Medium sized cysts 20%
  - Type III: Small cysts 10% evenly distributed in bulky lung
- Unilateral condition
- Middle or upper lobes affected
- High risk of malignancy → lobectomy
- CXR: Cystic over distension of lungs
- Associated with:
  - Prune belly syndrome
  - Hydrancephaly
- D/D
  - Lobar emphysema
  - Diaphragmatic hernia

5. Ectodermal dysplasia

A group of enherited conditions with primary defect in two or more of the followings:

- Teeth, nails, sweat glands and
- Tissues of ectodermal origin like eyes, ears, oral & nasal mucosa, melanocytes and CNS
- Management: multidisciplinary approach
- Cosmetics – for sparse hair
- Dental – early use of prothesis
- Hypohydrosis – activity, clothing, cooling
- Atopic eczema – emolient
- Eye abnormalities – ophthalmologist – artificial tears
- Sever respiratory problems – antibiotics, physio, regular follow-up

6. Congenital lobar emphysema

- Over inflataion of one or more lobes occurs secondary to broncheal obstruction or deficiency of broncheal cartilage
- LUL or RML are commonly affected
- Signs of respiratory distress with wheez
- Boys > girls (2:1)
- CXR: Lobar opacification due to fluid trapped beyond obstruction. Later affected lobe becomes over distended and leads to mediastinal shift
- Bronchoscopy – needed for diagnosis and removal of obstruction
- For slight symptoms → conservative management – CPAP
- For presistant respiratory failure → surgical excision of affected lobe
- About 30% have CHD

7. Alpha 1 antitrypsin deficiency (Nelson p1781 & 1679)

Consider in differential diagnosis of chronic pulmonary disease in childhood; obstructive jaundice in NN, cirrhosis in children & adults and combined hepatic and pulmonary dx in childhood and adolescence

- Alpha 1 antitrypsin
    - Is a protease inhibitor – synthesised by liver
    - Protects lung alveolar tissues from distruction by neutrophil elastase
    - Is necessay for in activation of proteolytic enzymes released from dead bacteria or leukocytes in lungs
    - Deficiency leads to → increased concentration of proteolytic enzymes → distruction of pulmonary tissue → emphysema
- The most common allele of protease inhibitor (Pi) system is M, and normal Phenotype is PiMM.
- The Z allele predispose to clinical deficiency; pts with liver disease are usually PiZZ and have serum alpha 1 antitrypsin levels < 2 mg / ml
    - Liver: PiZZ, PiSZ, PiZI
    - Lungs: PiZZ, PiSZ, Pi (null) and are associated with alpha 1 antitrypsin defiency that is responsible to cause emphysema
- Lab diagnosis

    - Serum levels of alpha 1 antitrypsin (N 180 – 280mg/dl)
    - Serm electrophoresis reveals – phenotype
    - PCR reveals – genotype
- CXR: Overinflatation with depressed diaphragm
- CT: Hyperexpansion in lower lung zones with occasional brocnchiectasis
- Treatment:
    - Enzyme replacement: 60 mg/kg/iv weekly
    - Standard supportive therapy
        - Aggressive treatment of pulmonary infection
        - Pneumococcal and influenza vaccines
        - Bronchodilators

8. Allergic bronchopulmonary aspergillosis

- It occurs in prolonged neutropenia; bone marrow transplanation and HIV infection
- Histoplasmosis and aspergilosis will give chronic inflammation and granuloma formation and have massive hepatosplenomegaly (tut in B1E)

Criteria for diagnosis

1. Episodic or chronic bronchial obstruction (asthma, CF)
2. Pulmonary infiltrates (recurrent, transient or fixed) @ upper lobes or hilar areas
3. Immediate skin reactivity to aspergillus antigen
4. Increased IgE
5. IgG against aspergillus antigen
6. Central/proximal bronchiectasis

Features helpful in diagnosis

- Hx of expectorating brown flecks/plugs
- Clinical features: Fever, cough, chest pain, tachypnoea and rapid deterioration
- CXR: Nodular changes and cavitation
- CT: Sensitive
- BAL: Aspergillus hyphae
- Lung biopsy is definitive
- Serum IgG against aspergillus antigen
- IgE: raised
- Positive sputum culture for Aspergillus Fumigatus
- Arthus-type reactions to antigens from Aspergillus fumigatus

Treatment

- Ampho B
- 5 flucytosine NA in SA
- Corticortisteroids are the most effective therapy – readily reduce symptoms & improve chest X rays
- Expectorants & chest physio – very helpful
- Neupogen in neutropenias
- Surgery on focal lung lesions

9. Cystic fibrosis (B Nelson p650)

- **Indications** for suspecting CF
  - FTT in infancy
  - Meconium ileus
  - Prolonged neonatal jaundice
  - Malabsorption
  - Steatorrhea
  - Recurrent rectal prolapse
  - Childhood cirrhosis
  - Heat prostration
  - Hyponatraemia
  - Hypochloraemia in infants
  - Metabolic alkalosis in older children

- **Do sweat tests on all children with:**
  - Unexplained chronic cough
  - Recurrent/chronic pneumonia
  - Nasal polyps

- **Diagnosis**
- **Sweat Test:** Analysis of sodium and chloride concentrations in sweat collected after stimulation with pilocarpine by Pilocarpine Iontophoresis with Cl > 60 mmol/L. May get false positive with:
  - Adrenal insufficiency
  - Diabetes insipidus
  - Glycogen storage dx
  - Hypohydrotic form of ectodermal dysplasia

  False negative
  Mutation found in patients with nornal sweat chloride concentration:
  3849+10kb C>T
- **Other tests:**
  - Screening meconium for elevated albumin
  - DNA –analysis for
    - Delta F508 (White population)
    - 3120/G-A mutation (African population)
  - Low levels of stool elastase
  - Measurement of bioelectrical potential differences across nasal epithelium

- **Counseling of parents:** 1 child with CF → risk for each subsequent pregnancy resulting in CF → 1:4. Each sibling has a chance of being a carrier → 66%. Males may be sterile

10. Bronchiestasis

Etiology

- Sputum culture usually yields Staph aureus, Strep Pn, H Infl, Pseudo and E. Coli
- After several antibiotic courses – get E. coli, Proteus, Klebsiella
- Main organisms in CF: Staph and Pseudomonas
- Bronchiectasis infrequently is associated with chronic maxillary sinusitis; each may contribute to the chronicity of the other. Staph, Strep, Bacteroides may infect the sinuses
- Bronchiectasis may occur in post measles, adenovirus and pertussis infections – incidence depends on incidence of these infections
- Bronchiectasis also occurs in
    - CF
    - Immunodeficiency states
    - Kartageners
    - Alpha 1 antitrypsin deficiency
    - and occasionally in severe asthma

Symptoms and signs

- Chronic cough
- Purulent sputum
- Recurrent respiratory infections
- Crackles over affected lobes
- Wheez and digital clubbing

Cardinal features/pathophysiology

- Dilatation of bronchi with bronchiolar wall destruction due to accumulation of purulent secretions and obstruction of airway
- Loss of ciliated epithelium and airway elastic tissue + oedema + chronic inflammation
- **Classification**: cylindric, varicose and saccular – does not corelate with etiology
- Saccular Bronchiectasis is an irregular bronchial dilatation, narrowing is irreversible → Cystic Bronchiectasis
- Usually acquired but may be familial based on genetic susceptibilities to infection, inflammation or Williams Campbell syndrome (congenital deficiency of bronchial cartilage leading to bronchiectasis).
- Suspect if acute LRTI's are slow to resolve, when there is a hx of recurrent pulmonary infection & when there is persistent atelectasis
- May be localized or diffused. If localized involve LLL, except in CF when RUL is the first & the most severely affected
- **Complications**
    - Malnutrition
    - Clubbing
    - Hypoxaemia
    - PHT
    - Cor-pulmonale

  - Clubbing may occur with localized lesions & may disappear when are resected
  - Empyema
  - Bronchopleural fistula
  - Metastatic brain abscesses
- **Severity of disease**
  - Mild dx – normal x rays or increased linear markings
  - Progressive dx – small cystic and nodular lesions lead to a honeycomb pattern
  - Advanced dx – cysts and bullae which may be filled with air/air-fluid
- **Investigations:- directed toward conditions suspected**
  - Sweat test
  - Immune function studies
  - Oesophageal pH monitoring
  - Serum Alpha 1 antitrypsin concentration
  - CXR:
    - Peribroncheal thickening
    - Atelactasis
    - Persistant infilterates
  - High resolution CT: has replaced bronchoscopy as investigation of choice. This may show thickwalled and dilated bronchi – that are larger than their accompanying pulmonary artery – Signet ring sign with associated lobar or segmental collapse
  - Flexible bronchoscopy
  - broncheal stenosis, compression or FB
  - Analysis of mucocilliary clearance
  - Pulmonary function tests
    - Obstructive defect
    - Obstructive and restrictive pattern in advanced disease
- **Treatment**
  - Physio
  - Bronchodilators
  - Appropriate antibiotics for 2 -3 weeks prior to bronchography
  - Asymm. or advanced dx – medical management
  - Surgical Mx - if localized dx with:
    - Persistent or recurrent obstruction
    - Infection
    - Recurrent heamoptysis
    - FB

11. Primary ciliary dyskinesia (PCD)

- PCD is 3rd most common form of inherited chronic airway disease of caucasian children after CF and genetic immune deficiency states
- It comprises those respiratory disorders having in common the malfunction of airway cilia
- Cilia are finger like structures extend from surface of cells into lumens of airway which consist of cytoskeletal protein structures – 9 microtubules in pairs with additional central pair
- Peripheral pair can attach to the outer via bridges or dynein arm

Kartagener's Syndrome

- Triad of:
  - Dextrocardia with situs inversus
  - Chronic sinusitis & / agenesis of frontal sinuses
  - Bronchiectasis
- Dextrocardia without situs inversus will include other anomalies example:
  - Single ventricle
  - TGA
  - PS
  - VSD
  - ASD
  - Asplenia
- Other associated manifestations are:
  - Nasal polyps
  - Conductive hearing loss
  - Transient IgA deficiency
  - Mesangiocapillary GN with hypocomplementaemia
- Variable penetrance (AR)
- Male sterility
- Bronchiectasis without situs inversus → compatible with partial expression of a genetic trait with exogenous factors like infection producing an acquired pulmonary lesion
- A feature that is helpful in differentiating from CF – repeated bouts of acute otitis media or chronic serous otitis

12. Pneumonia in immunocompromised children (Forfar p786)

- Diffuse interstitial changes on CXR
  - Pneumcystis
  - CMV
  - Adenovirus
- Lobar consoliodation
  - Bacterial and fungal infection
- Nodular appearance, cavitation and abscess formation
  - Staph aureus & anaerobes
  - Fungal infection

Causative organisms

- Pneumocystis – organism cannot be cultured but identified in:
    - Sputum
    - Nasopharungeal aspirates
    - BAL fluid
    - Lung biopsy
- Virals
    - CMV
    - Varicella zoster
    - Herpes simplex
    - Adenovirus
    - Measles
- Fungal
    - Aspergillosus
    - Candida

Causative agents in effusions and empyema

- Steph aureus
- Streptococcus pneumonia
- Haemophilus influenza
- Group A Streptococcus

GASTROENTROLOGY

HEPATOMEGALY

Causes of hepatomegaly – (see Lecture Notes on Practice of Paediatrics, Part 1)

Salient points to note:

1. Normal habitus
   - Child: liver < 2 cm below costal margin
   - Infant till 6 months: liver upto 3 cm below costal margin
2. Examination of liver
   - Size and shape: liver span is measured from superior purcussed border to the inferior palpable edge in Right MCL
   - Tendeness
   - Consistancy – soft (spong), firm (rubber ball) , rock hard (stone)
   - Character of surface – smooth, nodular, irregular
   - Edge – rounded, sharp, irregular
   - Pressence or absence of pulsations, thrills, bruis
     - Liver pulsation is usually due to aorta's impulse – constrictive pericarditis, tricuspid regurgitation or stenosis
     - Thrill: AV malformation, Hydatid echinococcal cyst
3. History
   - Age of patient: at different ages diff etiologies are common:
     - Wilsons dx present at birth – hepatomegaly uncommon <6 month
     - Galactosaemia: at young age
   - Environmental and travel history
     - Visceral larva migrans – common in Southern USA – exposed to puppies and nursing bitches
     - Enamoeba histolytica - history of travel (maxico, south & central USA, far eastern countries) → will present with right upper quadrant pain, fever and toxicity, hepatomegaly
   - Nutritional history
     - PEM:
       - Kwash – due to inadequate protein but sufficient calories
       - Marasmics
     - Infants with Heriditary Fructose Intolerance – present @ 4-5 months of age with vomiting and jaundice + hepatomegaly → coincides with introduction of fruits into diet.
     - Infants with Galactosaemia – early presentation due to galactose found in milk
     - Hypervitaminosis – Vitamin A
     - Drug exposure – alcohol, paracetamol
     - Fe over load – blood transfusions, thalassaemia patients

SHORT NOTES

1. GALACTOSAEMIA (B Nelson p254)

- Two enzyme defects
  - Galactose 1 phosphate uridyl transferase deficiency
  - Galactokinase deficiency
- Five variants – Durate (50%), Rennes (7-10%), Indianna, Los Angeles, Negro

1.1 GALACTOSE 1 PHOSPHATE URIDYL TRANSFERASE DEFICIENCY

- AR
- Clinical features – striking in neonate fed milk:
  - Liver failure: bilirubinaemia, disorders of coagulation, hypoglycaemia
  - Disordered renal tubular function: RTA with acidosis, glycosuria and amino-aciduria
  - Cataracts early in life
  - FTT
  - Learning disorders later in life
  - Prone to gram negative septiceamia – E coli
  - Ovarian failure later in life

- **Lab diagnosis:**
  - With ingestion of galactose, plasma galactose and erythrocyte galactose 1 phosphate levels are increased
  - Increased hepatocellular enzymes – ALT & AST
  - Increased unconjugated or conjugated bilirubin
  - Decreased coagulation factors
  - Hypoglycaemia & albuminuria
  - Positive clinitest for reducing sugars
  - No reaction with glucose oxidase on urine dipstix
  - Hyperchloraemic metabolic acidosis – normal anion gap
  - Confirm diagnosis by reduction on erythrocyte galactose 1 phosphate uridyl transferase
  - The concentration of G1P Uridyl Transferase rarely returns to normal even after the treatment is begun
  - DNA testing for mutation in G1P uridyle transferase confrims diagnosis

Treatment

- Remove galactose from diet – treat with soya preps
- Watch for gram neg. infections
- Diet can be relaxed later in childhood
- Congenital cataracts and mild brain damage have occurred even when treated from birth
- Therefore eliminate galactose from diet of pregnant mother

1.2. GALACTOKINASE DEFICIENCY

- AR
- Galactose accumulates in body fluids – gets formation of galactitol which acts as an osmotic agent resulting in the formation of cataracts and rarely increased ICP
- Homozygous – neonatal cataracts
- Heterozygous – adult cataracts
- Treatment: lifetime elimination of galactose from diet

2. HEREDITARY FRUCTOSE INTOLERANCE

- Analogous to galactosaemia
- Deficiency of fructose 1 phosphate aldolase – resulting in intracellular accumulation of fructose 1 phosphate
- Get emesis, hypoglycaemia, severe hepatic and renal disease
- Remove fructose and glucose from diet
- Affected patients of spontaneously: avoid fructose contaning foods and have no dental caries

3. LIPID DISORDERS

3.1 Gaucher's

- AR, especially occurs in Jews
- Deficiency of glucocerebrosidase enzyme
- Three types:

Type I – most common (99%), no neurological deficit

- Hepatosplenomegaly results from engorged macrophages.
- Splenomegaly results in thrombocytpaenia and hepatomegaly is accompanied by fibrosis and abnormal hepatic function
- Bone findings include flaring of distal femur (classic sign on X ray = Erlen Flask deformity). Complications include aseptic necrosis of head of femur, bone infarcts, pathological fractures and bone crisis (pain, swelling, fever)

Type II – fulminating disorder with CNS signs

Occurs in < 1 years with occulomotor apraxia, hypertonicity, strabismus and retroflexion of head – death by age <18 months

Type III – similar to type II but occurs later

Juvenile form with late onset neurological signs and long course

Diagnosis

- Leucocyte B-glucosidase activity. Bone marrow not necessary – if done – see crumpled tissue appearance. Increased serum acid phosphate and ACE
- Common mutations: nucleotides 84, 1226, 1448 at cDNA detected by PCR. Used for prognostic information and genetic counseling
- Complications – lymphoproliferative disorders (multiple myeloma & CML)

Treatment

- Splenectomy corrects thrombocytopaenia and aneamia, eliminates distress from marked organ enlargement
- Partial splenectomy
- Enzyme replacement – chemically modified mannose terminated glucocerebroside. Recombinant enzyme replacement
- BMT
- Gene transplant

3.2 Nimann Pick (classic form)

- Deficiency of sphingomyelinase (SM)
- Sphingomyelin accumulates in foam cells of RES of liver, spleen, lung , bone marrow and brain neurons
- Get mental retardation, myoclonic seizures, hypotonic, HSM, jaundice and cherry-red spots within 1 year
- Diagnosed by foam cells in the marrow and SM enzyme deficiency in WCC and skin fibroblasts

4. HERDITARY TYROSINAEMIA

Heptaomegaly, FTT, diarrohea, vomiting, rickets, cirrhosis

5. GLYCOGEN STORAGE DISEASE

- Abnormal concentration and structure of glycogen:
- Features include hepatomegaly, muscle weakness, acidosis and hypoglyceamia
- Types 1,6,8 – hepatomegaly only
- Types 5, 7 – muscle only
- Types 2,4 – various tissue – bad prognosis
- Types 3,10 – hepatomegaly and muscle
- Types 8 – CNS
- Types 11 - rickets

Glycogen synthetase deficiency

- Presents with convulsions, hypoglyceamia, acidosis, hyperketoneamia (ketones in urine). DD: ketotic hypoglycaemia

Type 1: Glycogenosis - Von Gierkes disease

- G 6 phopshatase deficiency
- Present with hepatomegaly at birth or soon after. Other symptoms are:
    - Protuberant abdomen
    - Hypoglycaemia
    - Ketosis
    - Lactic acidosis
    - Chubby facies
    - Short stature with or without renal enlargement
    - Convulsions
- Mentally normal, has hyperuriceamia and bleeding tendencies

- **Test:** Glucagon stimulation test – lactic acidosis and a flat glucose curve
- **Management:**
    - Prevent hypoglycaemia, gastrostomy tube or small NG continuous feeds adding MCT's
    - Porto caval shunting
    - Diazoxide – inhibits insuline release from pancrease. Dose: 5-25 mg/kg/day divided into BD to TDS. S/E: hypotension, dizziness, nausea, vomiting, and weakness. Long term use hypertrichosis of lanugo type, fluid retention, tachyphylaxis
    - Do 6 monthly U/S because of increased incidence of hepatic carcinoma
- **Prognosis** – fare to good
- **Prenatal diagnosis:** not possible – enzymes not detected in amniotic fluid

Type 2: Pompes disease

- Lysosomal and glucosidase deficiency: Two types
- **Type 2a** – normal at birth, marked hypotonia, normal mentally, presents with CMO and intractable CCF and has hepatosplenomegaly. Death occurs in infancy.
    - **DD**: Amyotonia congenita
- **Type 2b** – later onset of muscle weakness. Variable expression. Associated with recurrent infarctions. No cardiac involvement
- **Type 2a & 2b** – get normal glucagon response curve with increased blood sugar. Prenatal diagnosis possible

Type 3: Forbes disease

- Debrancher enzyme deficiency - amylo1-6 glucosidosis - similar to type I but milder
- Presents with marked hepatomegaly, variable tone and variable cardiomegaly
- No acidosis or hypoglycaemia or hyper lipideamia
- Urinary catecholamines normal
- Prenatal diagnosis possible
- Fair to good prognosis
- Glucagon response 2 hours after the meal – similar to type I
- No cirrhosis
- Liver biopsy similar to type I
- 50% die before 2 years and 100% by age 4 years

Type 4: Anderson disease

- Due to deficiency of brancher enzymes – very rare
- Hepatosplenomagaly, portal fibrosis with cirrhosis, portal hypertension and ascites
- Steroids yield temporary response
- No hypoglycaemia or lactic acidosis
- Dies by age 4 years from liver and cardiac failure
- Liver transplant before cirrhosis
- Diagnosis: WCC enzymes; cultured skin fibrblasts
- Best way: liver biopsy

Type 5: Mc Ardles

- Due to muscle phosphorylase deficienecy
- Presents with pain on exercise in skeletal muscle
- No increased lactate from ischaemic exercise
- No mental retardation
- Myoglobineamia
- Normal urinary cats
- Prognosis fair to good with sedentary life style
- Diagnosis?
- Muscle biopsy

Type 6: Hers

- Due to liver phosphorylase deficiency
- Massive hepatomegaly
- Usullay asymptomatic and live normal lives
- Glucagon test – flat response
- Hepatic enzyme assays

Type 7: Tarui

- Muscle phosphofructokinase deficiency
- Muscle pain and cramps
- Like Mc Ardles but milder form

Type 8

- Similar to G6PDD
- Presents with CNS disease with ataxia, nystagmus, truncal tremor, hypotonia
- Get de-acativated liver phosphorylase
- Increased urinary cats, Glucagon tolerance test increased

Type 9

- Liver phosphokinase deficiency
- Massive hepatomegaly
- Normal glucagon tolerance test
- Similar to type 6 which has a flat curve

Type 10

- Cyclic 3,5 AMP dependent kinase
- Massive hepatomegaly – similar to type 9
- Flat response to glucagon test
- No hypoglycaemia or cardiac involvement
- Mild recurrent muscular pain

Type 11: Rickets

- Hepatomegaly
- Stunted
- Hypophosphatemic rickets
- Treatment – PO4 and 1 alpha vit D

Investigations of suspected GSD

- Blood glucose, UE: look for increased anion gap (lactate)
- DNA mutation testing in blood cells. When this is feasable invasive procedures like liver / muscle biopsy can be avoided
- When mutation testing is not available do enzyme measurements in the tissue suspected to confirm diagnosis – leukocytes enzyme levels and glycogen stores in RBC
- Skin fibroblasts
- Muscle bx
- Liver biopsy: non specific: increased glycogen and pseudoglandular formation
- Paucity of lipid content esp type 4
- Urinary cats
- EMG & ECG: pathognomonic of type II
- Galactose stimulation test
- Glucagon stimulation test

Glucagon stimulation test:

Starve patient & give IV glucagon

- In types 2, 8, 9 – get normal response that is increased glucose and lactate
- In 1, 3, 6 – get flat response. Feed patient. Repeat test 2 hrs post prandial
- Repeat test – get increased glucose in type 3. Do glucose level monitoring 2 hrly

Prenatal diagnosis

- Usually AR except for 9b – sex linked recessive
- Assay of cultures amniotic fluid cells
- In I – no prenatal diagnosis
- 1, 3, 6, 9, 10 lead normal lives – therefore prenatal diagnosis not needed

Treatment

- Treatment of hepatic GSD is carried at maintaining satisfactory blood glucose levels or supplying alternate energy sources to muscle
- In type 1: nocturnal intragastric feeding of glucose during 1 or 2 years – thereafter snaks or nocturnal intragastric feedings of uncoocked corn starch – but hepatis tumours are threat
- Pompe type 2: enzyme replacement
- No specific treatment of disaeses of muscle

6. SCHISTOSOMIASIAS – BILHARZIASIS (B Nelson p563)

- 5 types, 3 common – S heamatobium, S mansoni (common in Africa), S japonicum
- Fresh water snails are intermediate host
- Bladder granuloma – renal failure & carcinoma bladder
- Syndrome of fever, malaise, cough, abdominal pain & rash can occure with 3-12 weeks of infection while worms are maturing
- Intestinal form lead to ulceration, colic, abdominal pain & diarrhea
- Hepatomegaly – mainly left lobe. Para-sinusoidal liver obstruction with hepatosplenomegaly
- Portal hypertension and primary pulmonary hypertension, ascites, haematemesis
- Katayama fever (an acute condition with fever, weight loos, HSM & eosinophilia)
- Diagnosis – eggs in stool or urine
- Treatment – praziquantel
- Prevention – sanitary measures, moluscocides & therapy for infected individials

7. HYDATID DISEASE (B Nelson p564)

- Unilocular cystic disease caused by larval stage of Echinococcus granulosus
- Humans → intermediate host
- Embryo passes through intestine to liver and other organs
- Cysts > 2cm diameter
- **Clinical features** are due to space occupying cyst
    - Lung
        - Heampotysis
        - Cough
        - Dysnopea
        - RDS
    - Brain (appear as tumors)
    - Hepatic (compress & obstruct blood supply)
- **Diagnosis** by ultrasound – serology is helpful
- **Treatment:** surgery for large cyst. Some benefit from mebendazole / albendazole
- **Differential diagnosis:**
    - Cong cysts
    - Traumatic cyst
    - Inflammatory cysts
    - Obstruction to outflow tract

8. TUMOURS OF LIVER (Coovadia p468)

- Two main primary malignant tumors – Hepatocellular ca and Hepatoblastoma
  - Present with abdominal swelling
  - Enlargerd irregular firm liver which may be tender
  - Increased alpha feto protein in 80%
- Hepatocellular carcinoma (post hep B – CAH)
  - Rare < 6yrs
  - Routine vaccination of HBV will reduce the incidence of HCC
- Infantile choriocarcinoma – Germ cell tumor
  - Young infants
  - Hepatomegaly
  - Aneamia
  - Haemorrhage
  - Chorionic gonadotrophin increased in urine
- Hepatoblastoma or embryonal cell carcinoma
  - Predominates in males
  - Occures generally < 3years of age
  - Right lobe usually involved
  - Other anomalies – hemihypertrophy and virilization
- Heamangioma, haemagioendothelioma
- Leukemia
- Hodgkins
- Metastatic neuroblastoma esp. type IV

9. HYDROPS FOETALIS (Coovadia p143/ Neonatology Cloherty et al p206)

Grossly oedematous foetus which is born with:

- Anaemia & HSM
- Ascities & pleural effusions

Causes

- Rh disease
- Syphilis / CMV / Toxo
- CCF
- Hypo proteinaemia – due to hepatic and renal disease & twin to twin transfusion
- Thalasaemia
- Asphyxia

Management

1. Respiratory support
2. Removal of ascitic fluid + pleural effusion – if contributing to respiratory embarrasment
3. Slow correction of anaemia with exchange transfusion
4. Lasix for CCF
5. Vitamin K for haemorrhage prevention
6. Treat hypoglycaemia

10. BUDD CHIARI SYNDROME

Occurs with obstruction to hepatic veins anywhere between the efferent hepatic veins and the entry of IVC into right atrium. In most cases no specific cause can be found but thrombosis can occur from inherited and acquired hypercoagulable states
Other causes:

- Complications of hepatic or metastatic neoplasms
- Collagin vascular disease
- Infection and trauma
- Behcet syndrome
- Inflammatory bowel disease
- Aspergillosis
- Dacarbazine therapy
- IVC webs

Veno-occulsive disease is most frequent cause of hepatic vein obstruction in these children (centrilobular venules or sublobular hepatic venis). This disorder occurs after total body radiation with or without cytotoxic drug therapy that is commonly used before bone marrow transplantation. It also occurs after herbal teas ingestion – containing pyrrolizidine alkaloids.

11. REYE'S SYNDROME

- Involves hepatic dysfunction and encephalopathy
- Typically occurs after viral infections (influenza B & varicella) and is associated with use of aspirin during the illness
- When prodromal symptoms are resolving there may be rapid deterioration with sever emesis and mental state changes → delirium → coma
- Minimal or absent jaundice, hepatomegaly in 50% cases
- 7 stages ac to CDC classification (0-6)
- Complications: brain herniation, status epilepticus, SIADH, and DI, ac resp failure, cv collapse, GI bleeding, ARF, sepsis & death
- DD: Encephalitis, meningitis, IEM, hepatitis, intracranial haemorrhage, intussusception, or drug toxicity
- Work up: exclude IEM, CT head (cerebral oedema), EEG (slow wave activity in early stages and flattened waves in late stages)
- Lab confirmation (Ziai p48). Raised ammonia, urea, cratinine, ALT, AST. Prolonged PT, aPTT. Elevated lipase and amylase levels. Do blood gas to evaluate metabolic acidosis. Increased urine SG and ketonuria

12. CHOLEDOCHAL CYSTS

These are congenital dilatations of common bile duct that can cause progressive biliary obstruction and billiary cirrhosis

TYPES:

- Dilatation of a portion or entire CBD (type 1)
- Diverticulum of CBD (type 2)

- Dilatation of intradudinal portion of CBD (type 3)
- Multiple dilatations of intrahepatic & extrahepatic biliary tree (type 4)
- Cystic dilataion of intrahepatic biliary ducts (type 5 or Caroli's dx)

Pathogenesis

- Not certain – some reports suggest at junction of CBD and pancreatic duct before their entry into syphincter of Oddi may allow reflux of pancreatic enzymes into CBD causing inflammation → weakness → dilatation of CBD
- As part of infection process – Reovirus has been isolated in some patients with choledocal cysts

Signs and symptoms

Infants: cholestatic jaundice, ascities, coagulopathy and rarely palpable mass
Older child: triad of abdominal pain, jaundice, mass: occurs in 33% pts

Features of acute cholangitis

- Fever
- Right upper quadrant tendeness
- Jaundice
- Leukocytosis

Diagnosis

- US abdomen
- Prenatal diagnosis has been made
- Magnetic resonance cholangiography is useful in preoperative assessment of choledochal cyst anatomy

Treatment

- Primary excision of cyst
- Roux-en-Y choledochojejunostomy

Complications

- Post operative recurrent cholangitis or stricture

13. CAROLI DISEASE

Cystic dilatation of intrahepatic bile ducts: Two varrients:

Caroli disease

Ectasias of IHB ducts without other abnormalities

Caroli syndrome

Congenital duct dilatation is associated with featutes of congenital hepatic fibrosis and renal lesions of polycystic renal disease (AR)

14. HISTIOCYTOSIS (Nelson p2159)

The term histiocytosis referrs to disorders of the mononuclear phagocytic system
Calassified as follows:
Class I: Langerhans cell histiocytosis
Class II: Sinus histeocytosis
Class III: Acute monocytic leukemia

15. OSLER – RENDU – WEBER SYNDROME

1. AD
2. Also called as heriditory haemorrhagic talangiectasia (Ziai p631)
3. Multiple spider & nodular telengiectasias distributed over
   - Face
   - Oral mucosa
   - Conjunctiva
   - Finger tips
   - Nail beds

Pts have multiple episodes of bleeding because of involvement of
- GIT
- Bladder
- Lungs
- Liver
- Brain

CLINICAL SYNDROMES ASSOCIATED WITH HEPATITIS

Acute hepatitis:
It is sometime associated with intrahepatic cholestasis

Fulminant hepatitis:
It is associated with massive necrosis - has a high mortality rate

Chronic viral hepatitis
May lead to carrier state without or with continuing hepatic necrosis

Chronic hepatitis
Associated with continuing necrosis often progresses to cirrhosis whereas that associated simply with a carrier state does not

(Reference: Chandrasoma et al. Concise pathology: 3rd edition Appleton & Lange 1998)

CAUSES OF HEPATOMEGALY (in different age groups)

NEONATES

1. Erythroblastosis foetalis
2. Neonatal hepatitis – idiopathic
3. Congenital infection
4. Peri/post-natal infection – bacterial septicaemia, meningitis, viral, Coxsackie, hepatitis A & B
5. CCF
6. Bililary atresia
7. Haemangiomas
8. Choledochal cyst

INFANTS

1. PEM
2. CF
3. CCF
4. Metabolic
   - Galactosaemia
   - Metabolic storage dx
   - A1 ATD
   - Lysosomal storage dx
5. Histiocytosis
6. Tumours – liver, neuroblastoma, Wilms tumor

YOUNG CHILDREN

1. PEM
2. CF
3. Toxins/drugs like INH
4. Parasites – amoebiasis, schistosomiasis, hydatid cyst
5. Tumours
   a. Primary – leukemia, NHL
   b. Secondary – Wilms, neuroblastoma, rhabdomyoma
6. Reyes syndrome

OLDER CHILDREN & ADOLESCENTS

1. Hepatitis A, B, CAH, EBV
2. Liver dx associated with inflammatory bowel dx
3. Drug and alcohol hepatitis
4. Metabolic – Wilsons, cystinosis, amyloidosis
5. Heamochromatosis – primary or secondary to transfusion
6. Lipidosis especially juvenile, Gaucher's disease
7. Tumours
   a. Primary → Leukemia, NHL, Hodgkins dx,
   b. Secondaries from any primary tumor

HEPATOMEGALY WITH HYPOGLYCAEMIA

1. Massive hepatic necrosis
2. Glycogen storage dx
    - Gluc 6 phosphatase deficiency – type I
    - Amylo 1-6 glucosidase deficiency – type II
    - Phosphorylase deficiency – type IV
3. Galactosaemia
4. Reyes syndrome
5. Hereditary fructose intolerance
6. Fructose 1-6 diphosphatase deficiency

ASCITES

- When upright – hypogastrium most distended, when in dorsal decubitus position, flanks bulge, stretching of outer abdominal wall results in tense shiny skin, dilated abd vessels $\pm$ umbilical hernia
- Shifting dullness and fluid wave sign occurs when there is > 500ml ascites, though an over abundance may mask the sign
- 120 ml fluid can be diagnostic using the puddle sign

SPLENOMEGALY

Causes of splenomegaly see Lecture notes on Paediatric Clinical Examination (Practice of Paediatrics part1)

Salient points to note:

1. Spleen: in 15-30% normal neonates is easily palpable when abdomen is relaxed
2. It is smooth, notched and will not have overlying bowel
3. It incrsaes in size – growthfrist moves in posterior direction – all under rib cage – when palpable it has increased by 2-3 timws it normal size
4. Percussion is done in anterior axillary line in the lowest intercostal margin (8^{th} and 9^{th}). Note should be resonant – remains so with inspiration. Dullness or a change to dullness implies a degree of spleenomegaly.
5. Children with chronic pulmonary disease (sever asthma, CCF) may have air traping and unusually flat diaphragms :: more easily palpable spleen

Summary of an approach: (Ziai p348)

Careful family history
- Heriditary anaemias
- Metabolic disorders

History of travel to malaria endemic areas → malaria

Failure to gain weight and height – more chronic conditions

Examination
Jaundice → haemolytic anaemia / liver disease
Fever accompanied by chills and exanthem → infectious etiology
Arthritis → collagen vascular disease – accompanied by bleeding → leukaemia
Cataract + mental retardation→ galactosaemia
HSM with portal hypertension → congestive etiology

GROUPS OF COMMON CONDTIONS FOR ENLARGED SPLEEN

HAEMATOLOGICAL

- **Anaemias** with extramedullary heamopoesis and RES hyperplasia
  - Cause may be congenital/acquired, haemolytic anaemia or heamoglobinopathy including thalassemia
- **Infections**
  - Bacterial – septicaemia, typhoid, endocarditis
  - Viral – EBV, CMV
  - Protozoal – malaria, toxo
- **Congestive splenomegaly – Banti's dx**
  - Secondary to portal/splenic vein obstruction

    - Secondary to intrahepatic dx e.g. cirrhosis, chronic congestive heart failure
- **Infiltrations** – Lipidosis, Nieman Pick, Gaucher's, non-lipid reticuloendotheliosis
- **Cysts** – congenital (epidermoids) or acquired (pseudocysts)
- **Neoplasms** – leukemia, lymphosarcoma, Hodgkins, haemangioma, lymphangioma
- **Miscellanous** – Still's dx, RA, SLE
- **Tropical splenomegaly** – hyper gammaglobulinaemia ?recurrent malaria

MALARIA

- Get splenomegaly with vivax then falciparum infections
- Get perisplenitis infarction and even rupture
- Repeated attacks lead to a hard large spleen
- Idiopathic splenomegaly → big spleen dx of Africa – due to abnormal response to plasmodium malariae in malnourished children
- Enlargement of spleen – accompanied by lymphocytic infiltration of liver sinusoids

GAUCHER'S

- Greater splenomegaly than hepatomegaly

CHRONIC MYELOCYTIC LEUKEMIA

- Uncommon in paeds
- Accounts for only 3% of cases of leukemia in children
- Insidious onset – firm large splenomegaly as far as pelvis
- Juvenile type: CML < 2 years. Have eczematoid rash, LN, recurrent bacterial infections, moderately increased hepatomegaly and some splenomegaly. Monocytosis prominent

TWO MONTHS OLD CHILD WITH HEPATOSPLENOMEGALY

CAUSES

INFECTIONS

Congenital

- Toxo: Jaundice, HSM, hydroceph / microceph, chorioretinitis
- Rubella: Jaund. HSM, blue berry muffin rash, cataracts, cardiac dx, celery stalk lesions
- Parvovirus
- Herpes
- CMV – microceph, chorioretinitis, rash
- Syphilis, maculopap rash, bullae, peeling skin, HSM, X rays, pseudoparalysis
- HIV
- Listeria
- GBS

Acquired

- Bacterial septiceamia
- Viral – CMV, EBV, parvo
- Hydatid, amoebiasis, bilharzia
- Fungal, histoplasmosis, coccio

BLOOD DISORDER

- Congenital red cell aplasia, Pearson marrow p

MALIGNANCY

STORAGE DISEASE

- Glycogen, lipid, mucopolysacch

STRUCTURAL ABNORM

- Bil atresia
- Choled cyst

APPROACH

- Well looking
- *Structural anomalies*
- *Leukemia*
- Ill looking
- *Infections*
- *Storage diseases*
- Stool colour
- Urine colour
- Cirrhotic liver
- Dysmorphic?
- Features of chronic liver dx
- Firm liver, oedema, ascites, fits/ neurological abn, bleeding disorder
- If obstructive – deep jaundice, xanthoma, pruritis, lack of vitamins ADEK

INVEST & MANAGEMT

FBC

- Infection
- Leucoerythroblastic picture – syphilis
- Haemolysis – Donath Landsteiner syndrome
- Hypersplenism?

LFT - ? hepatitis, ?obstructive

TORCH screen

PI/PTT – liver function

U/S head

- Periventricular calcification, CMV, intracranial calcification, toxoplasmosis

U/S liver

Bil atresia, choled. cyst

Liver bx

Infection, billiary atresia, storage dx, leukemia

Bone marrow

6 YEARS OLD CHILD WITH HEPATOSPLENOMEGALY

CAUSES: INFLAMATION

1. Infection

Acute – septicaemia, parvovirus, liver abscess, amoebiasis/bacterial

Chronic: Parasites- bilharzia, malaria, toxo, Viral – cmv, ebv, Coxsackie, echo, hepatitis , hiv, TB, Rickettsiae, Fungal

2. Auto imm dx of liver

3. Drugs and toxins

4. Billiary tract obstruction

RET ENDOTH SYST HYPERPLASIA

- > 10% Kupffer cells:
- Septiceamia

Malignancy

- **Primary** with portal ht, hepatoma, hepayoblastoma, heamangioma, heamangioendothelioma, histiocytosis, infantile chorioca.
- **Secondary** – leuk. Neuro, type IV Hogkins, nephro, osteosarcoma, Ewings, rhabdomyo

Granulomatous reactions

- TB, sarcoid

Anaemia

- Anaemia except aplastic – Fe defic. Heamolytic, meg, malign, chronic heamolysis, hered spherodcytosis, cold/warm agglutinins, thalassemia

SPACE OCC LESION & INFILTRATIONS

- Abscess
- Neoplasm
- Chronic infection
- Connective tx dx – sarcoid, SLE, polymyositis, dermatomyositis, parvomyo, Wegeners, myeloid
- Vascular malformations/ thrombosis
- Venous congestion: Budd Chiari, veno occlusive dx, CCF, constrict. pericarditis, pericardial effusion
- Storage disorders: CHO, AA/ protein, lipid, (G N-P), Wilsons, fat (Kwash, Reyes, Mauriac, CF, drugs)

APPROACH

- True or apparent HSM
- Sick looking→acute /infectious
- Ingestion of bush tea/hx blood transfusions
- Escerifications. priritis, mantoux, BCG
- Signs of chronic liver dx – clubbing, oedema, firm/hard liver, pallor, leuconychia, upper and lower borders liver, lobes/surface, edge of liver, bruits, subhepatic masses
- Signs of portal HT – portal v pressure >25cm, varices, ascites, oedema, splenomegaly, anaemia, heamatomesis, malaena, distended abdo veins
- Other signs of TB, CF, A1AT defic (Chest), connective tx disorder
- Bleeding tendencies, bony tenderness
- Abdominal masses
- CVS exam: pompes, chronic CCF
- ? liver failure – sensorium, flap, hypoglyc, foetor
- Eyes – KF rings, cataracts
- Neuro mx exam: pompes
- Growth
- Urine: red substances, pH (exclu. RTA)
- PR

INVESTIG & MANMT

BLOOD

FBC and diff.

Exclude infection heamatological abnormality, malignancy

Viral screen

LFTs

- ?hepatitis ?obstruction
- albumin (liver function)

PI/PTT

- liver function

U/E

- metabolic acidosis, renal function

HbElectroph: thalassemia

GM/Gluc

- hypoglycaemia, mantoux, gastric washings

Radiological

CXR excl. TB and CVS problems

US abdomen, bone survey

Urine - dipstix, red substances, schisto., protein

Stool: colour

APPROACH TO A CHILD WITH HEPATOSPLENOMEGALY

Summary of pathophysiological mechanisms:

1. **Inflammation** – jaundice often present
2. **Kupffer cell hyperplasia** (RE cell) with TB or other generalized infections
3. **Congestions** – exclude cardiac causes
4. **Cellular infilterates** – usual with bleeding tendancies, lymphadenopathy and anaemia
5. **Storage products** – usually abnormal appearance, neurological signs and marked firm enlargement of liver and spleen.
6. **Fatty infilteration** – typical Kwashiorkor and malnutrition
7. **Space occupying lesion**
8. **Metabolic**

CAUSES

1. **INFLAMATION:** Abnormal liver FTs
   - Infections – acute sick child, soft hepa, chronic, i.e TB
   - Neonatal and congenital : CMV, HSV, toxo, rubella, syphilis, listeriosis
   - Viral hepatitis: Hepatotrophic and other general viral infections (EBV, HIV)
   - Parasitic infection: Hydatid disease, amoebiasis, bilharzia (left lobe), toxo
   - Fungal: Histoplasmosis, cocciodomycosis
   - Auto immune disease of liver
   - Toxic and drug interactions
   - Biliarry tract obstruction

2. **RETICULOEDOTHELIAL:**
   - Kupffer cells comprise 10% of normal liver, blood cultures, cxr, biopsy may be needed
   - Septiceamia
   - Malignant disease – lymphoma, leukemia, neuroblastoma, Langerhans cell, histiocytosis,
   - Granulomatous response – TB, Sarcoidosis
   - Aneamia – hemolytic, megaloblastic, Fe def. except aplastic

3. **VENOUS CONGESTION:** Portal hypertension will result in splenomegaly in many of the conditions causing hepatomegaly.
   Need CXR and cardiac U/S
   - Congestive heart failure
   - Pericardial effusion or constrictive pericarditis
   - Budd Chiari (acute onset of ascites)
   - IVC valves

4. SPACE OCCUPYING LESION

- Examples: abscess, secondary and primary neoplasms
- Need CT scan/isotope scan/ultrasound

5. INFILTERATIONS:

- Need to do haematological investigation, liver / bone marrow biopsy
- **Eerythroblastosis:** Rh incompatibility, thalassaemia
- **Lymphoma**
- **Leukemia**
- **Histocytosis syndrome**
- **Connective tissue disorders** – SLE, dermatomyositis, JCA, Wegeners, MCT dx
- **Sarcoid, amyloidosis**

6. STORAGE DISORERS

- Liver and other tissue biopsy
- Crbohydrate storage dx (liver only) , galactosaemia
- Mucopolysaccharidosis
- Lipid – Gauchers, Niemann Pick, Tay Sachs
- Tyrosineamia

7. FAT ACCUMULATION

- Clinical diagnosis. Liver biopsy if doubt
- Malnutrition
- Hyperalimentation
- Cystic fibrosis
- Galactosaemia
- Uncontrolled diabetes mellitis: Mauriac syndrome
- Hepatotoxic drugs
- Reyes sydrome

8. METABOLIC DISORDERS

- Wilsons dx
- Cystic fibrosis
- Galactosaemia

ETIOLOGY REGARDING CONSISTANCY OF LIVER

Soft liver

1. Infections
2. Metabolic
3. Cardiac
4. Blood dycrasiasis/anaemias
5. Heamatological malignancies
6. Collagen vascular disease
7. Early in stage of storage dx

Firm liver

1. Granulomatous infiltration around portal tract:
   - Bilhrazia, TB, sarcoid, lymphoma, leukemia
2. Metabolic: Wilsons, Alpha 1 anti trypsin deficiency
3. Storage diseases
   - Carbohydrate (galactosaemia, GSD).
   - Lipids (Gauchers, Niemann Pick), fatty liver (Kwas. Reyes, Mauriac synd).
4. Chronic active hepatitis with fibrosis Hep B, C, CMV, autoimmune i.e. SLE

Hard liver

1. Billiary cirrhosis (due to bile duct obstruction):
   - Billiary atresia or hypoplasia
   - Choledocal cysts – cystic fibrosis
   - Ascending cholangitis – BD stenosis
2. Post necrotic – due to hepatocellular lesion
   - Post hepatitis – neonatal hepatitis, viral hepatitis , chronic hepatitis
   - Venous congestion - constrictive pericardiasis, CCF, Bud Chiari Syndrome, Veno-occlusive disease
3. Tumors

Massive liver

1. Budd Chiari: acute onset of ascities - absence of hepatojugular reflex
2. Veno occlusive dx - herbal medications (genus seneio pyrrolizidine alkaloids)
3. CCF/constructive pericardititis
4. Tumors – Hepatoblastoma, Hepatocellular carcinoma,
5. Cysts of liver – hydatid, schistosomiasis

Hepatomegaly with big spleen

1. Malaria
2. Gauchers
3. CML / Lymphoma
4. Myelofibrosis
5. Toxic
6. Splenic vein thrombosis
7. Portal hypertension

APPROACH TO LIVER DISEASE – IN OLDER CHILDREN

- **History** of
  - Ingestion of bush tea (veno occlusive dx), blood transfusion, bleeding
- **On examination:**
  - Sick or well?
  - Jaundice
  - Clubbing
  - Mantoux/BCG (TB live)
  - LN
  - Scarification marks
  - Anaemia
  - Foetar
  - Pruritis
- **Chest:** Exclude signs of TB, cystic fibrosis, alpha 1 antitrypsin
- **CVS:** Excl pericarditis, CMO (Pompes) type 2 GSD, chronic CCF→ hepatic insufficiency → due to chronic congestion
- **CNS:** Sensorium (liver failure), flapping tremor, KF rings, non-neuromuscular problems (Pompes)
- **Abdomen:** Distended, smiling umbilicus, ascites (shifting, dullness, fluid thrill, bulging flanks). Describe liver – upper and lower borders, extent, texture, subhepatic mass, lobes, surface, pulsations, bruits, edge. Describe spleen
- **Do PR** – pale stool, malaena

EXCLUDE LIVER FAILURE

- Foetar, flap, encephalopathy

EVIDENCE OF CHRONIC LIVER DISEASE

- **Synthetic functions:**
  - Oedema, hypoproteianeamia (albumin),
  - Bleeding (clotting factors)
  - Hypoglycaemia

- **Excretory functions:**
  - Bilirubin – jaundice - pruritis
  - Xanthomas
  - Drugs

- **Metabolic functions**
  - Bilirubin
  - Rickets
  - Anaemia
  - FTT
- **Gynaecomastia**, testicular atrophy, palmer erythema, spider naevi rarely in children < puberty due to increased oestrogens

- **Look for purpura** – anaemia, hypersplenism
- **Defence –** by Kupffer cells- increased gut infections
- **Storage –** glycogen, lipids, Cu, Fe, Vit A
- Sick child – think of malignancy, infections, chronic liver disease
- **Signs of portal hypertension**
  - Splenomegaly
  - Anaemia – haematuria, malaena
  - Ascites
  - Oedema
  - Distended abdominal veins and varices

1 MONTH OLD CHILD WITH JAUNDICE

<table>
<tr><th colspan="3">DYSMORPHIC</th></tr>
<tr>
<td>Alagilles
• Triangular face, braod forehead, deep set wide spaed eyes, small pointed chin, long straight nose
• Periph. PS or TOF, post
• Embryotoxin
• Skeletal abnormalities (butterfly veterbra, failure of fusion of vertebral arch)
• Renal tubulo-interstitial nephropathy
• Pruritis, xanthelasma, acholic stools, fat malabsorption
• Mx → for cholestasis
• Sx for pulm lesion</td>
<td>Zellwegers (absence of peroxisomes)
• Jaundice
• hypotonia
• seizures
• increased liver enzymes
• renal cortical cysts
• mongloid facies
• ocular abn cataracts, glaucoma, acorneal clouding, bruc/shfield spots, optic n dysplasia
• Skeletal abn. – stippled calcification of patella + greater trochanter.
• Diff diag → chondrodysplasia punctata</td>
<td>Downs
Trisomy 13,15
Hypothyroid</td>
</tr>
<tr><th colspan="3">NOT DYSMORPHIC</th></tr>
<tr><td colspan="3">UNCONJUGATED – ABO/ Rh, Breast milk jaundice

CONJUGATED – pale stools, dark urine
• Infections – syphilis, cmv, hep b, uti, rubella, herpes
• Metabolic/hereditary – galactosaemia, fructosaemia, Tyrosinaemia, A1ATD, CF, Gauchers, Niemann -Pick, Wilson’s, (5-20yrs), Byler (AR; progressive intrahep cholestasis with N chol and low GGT. Progresses to liver failure, cirrhosis, ESLD. Pruritis not in keeping with level of jaundice. Gilberts, Rotor
• Drugs – TPN
• Endocrine – Hypopituitarism
• Structural – Croli, choled cyst, bl atresia (progressive – excl. situs inversus, tris 18/13).
Increased liver enzymes.
Acq in utero/perinatal hepato-porto enterostomy before 2/12 → 80% success, > 9/12 →15% success, 5 yr survival → 30-60%. Late presentations/failed Kasai - transplant – 5 yr survival → 70%</td></tr>
<tr><td colspan="3">INVESTIGATIONS : Stool, Urine, LFTs, U/S liver and head, liver Bx to exclude CVS abnormality</td></tr>
<tr><th colspan="3">CHOLESTASIS</th></tr>
<tr>
<td><u>Obstructive:</u>
Bil. atresia, congenital bile duct anomalies, cholilithiases, cholangitis (primary sclerosing infection, associated with histiocytosis)</td>
<td><u>Bile duct paucity:</u>
Alagilles,
Non syndromic, ductopenic allograft rejection</td>
<td><u>Hepatocellular:</u>
Hepatitis, A1ATD,
Inborn errors, bile acid synthesis, TPN, Byler</td>
</tr>
</table>

INVESTIGATIONS FOR PROLONGED NEONATAL JAUNDICE

General investigations

1. FBC – search for sepsis
2. Retics
   - After 1st week > 30%
   - First day of life >10% is abnormal
3. Haematocrit
4. Coombs
   - Direct – Rh +
   - Indirect – ABO +
5. LFTs / TSB
   - Direct bili → increase confirms cholestasis
   - AST, ALT – hepatocellular injury
   - GGT – biliary obstruction
6. Blood/ urine/ CSF – mcs (septic screen)
7. TORCH + viral cultures: echo, paramyxo, parvo B19, EBV, coxach. Measles and varicella – if contact noted
8. Urine for CMV
9. Hepatitis screen

Special investigations

1. TSH, T4
2. Osmotic fragility for congenital spherocytosis
3. RBC enzyme essay→ G6PDD
4. RBC galactose -1- phosphate uridyl transferase → Galactosaemia
5. Alpha 1 antitrypsin levels – serum ceruloplasmin
6. Urine for reducing substances and organic acids
7. Serum aminoacids
8. Sweat Chloride & CF mutation analysis
9. Abdominal U/S
10. Hepatibiliary scintigraphy – to rule out biliary atresia, choledochal cyst
11. Liver biopsy

PORTAL HYPERTENSION

Increased verusus normal mesenteric blood flow or
Increased versus normal hepatic venous wedge pressure

Areas of collaterals

1. Rectal – in anal canal – heamorrhoids – malena
2. Oesophageal – haematemesis
3. Celiac and retroperitoneal
4. Caput medusa
5. Collateral: Portal vein, azygous vein via submucosal vein (varices) in stomach
6. Normal portal vein pressure = 15 cm H_2O, > 25cm = portal hypertension

Complications

1. Ascites
2. Splenomegaly
3. Bleeding varies
4. Encephalopathy

Mechanism

May be due to:

1. Increased resistance to flow which may be prehepatic, hepatic or posthepatic or
2. Increased flow in portal portal vein example AV fistula

CAUSES: (Coovadia p671)

Extra hepatic

1. Presinusoidal
   - Portal or spelnic vein obstruction due to:
     a. AV fistula
     b. Lymph nodes pressure
     c. External compression of portal vein
2. Post sinusoidal
   - Budd Chiari
   - Inferior vena cava obstruction
   - Pericarditis or heart failiure

Intrahepatic – sinusoidal (VACCS)

1. Veno-occlusive dx
2. Acute or chronic hepatitis
3. Cirrhosis
4. Congenital hepatic fibrosis
5. Schistosomiasis

Differential Diagnosis

PORTAL VENOUS THROMBOSIS

- Umbilical sepsis → PV thromobosis and obstruction → cavernous transformation of PV to common varices

BUDD CHIARI SYNDROME

- Syndrome of congested hepatomegaly, portal HT, acute onset ascites and varying degrees of liver failure due to acute obstruction of hepatic veins, IVC and its tributaries. Get tender hepatomegaly, ascites and jaundice. No hepato jugular reflex
- Risk factors – trauma, coagulopathies , sickle cell anemia, leukemia, polycythemia, hepatic abscess, irradiation, GVHD

Causes

- Heamotologic disorders – e.g: Polycytheamia rubra vera, paroxysmal nocturnal HB
- Disorders of coagulation e.g: Antithrombic III and other deficiencies
- Behcets: Oral and genital ulcers, uveitis
- Tumours: Intrahepatic, IVC e.g hypernephroma
- Congenital webs
- Trauma
- Idiopathic

Distinction from veno-occlusive dx:
VOD involves central, lobular and sublobular hepatic veins – sparing larger veins, it is not associated with thrombosis

Two types of disease entities

Oriental – characterised by webs, tromobosis and obstruction

- Caval web may be a membrane, stricture, and coarctation. Varying degree of thromobosis and obstruction, varying severity
- Chronic dx – not life threatening

West

- Acute illness - Underlying occult / iatrogenic/myeloproliferative. Thrombotic tendencies. May improve spontaneously or become chronic. Death if untreated early.

Investigations:

- LFT
- Ultrasound (abnormal confluence of HV, IVC, abnormal Doppler)
- CT scan, Technetium-99 isotope, Hepatic venography
- IVC pressures, Paracentensis (exudates >30g/l)
- Hepatic biopsy

Management

- **Western type** – thrombolytic Rx early, rapid deterioration – transplant, porto systemic shunting
- **Orient** – dilation with bouguise, web splitting, balloon angioplasty
- **Transplantation** – 30% mortality, indicated if despite compression, liver failure ensues
- **Mx of heamorrhage**
  - Children usually stop spontaneously
  - Uncontrolled bleeding may be due to thrombocytopeania or deficiency of clotting factors due to severe hepatocellular dysfunction
- IV vasopressin – constricts splanchnic veins and decreases portal vein pressure
- Balloon tamponade older children
- Endoscopic sclerotherapy
- Repeated sclerosing injections
- Porto caval anastomosis/ distal splenorenal shunt
- Portal HT produces hypersplenism, aneamia, thrombocytopaenia, neutropaenia

VENO OCCLUSIVE DISEASE

- Due to toxins example senecio alkaloids, herbal teas, cytotoxic drugs e.g thioguanaine, post BMT
- Insidious onset – obliteration of small hepatic veins
- In severe forms get jaundice, ascites, RUQ pain, oliguria, followed by encephalopathy and fulminant hepatic failure
- Very mild form → histoloigical diagnosis

Differential diag:

- Congestive CMO
- Constrictive pericarditis
- Budd Chiari
- TB peritonitis
- Thoracic duct obstruction
- TB thoracic duct obstruction will give exudates

CONGENITAL HEPATIC FIBROSIS (Nelson p1706)

1. Clinical onset in childhood presents with HSM, cholangitis or bleeding seconday to portal hypertension.
2. It is diffuse periportal and perilobular fibrosis in broad bands that contain distorted bile-duct like structures
3. Liver biopsy is required for diagnosis
4. Caroli dx and choledochal cyst have been associated – 75% have renal dx
5. It also occures as part of COACH syndrome
   - **C**erebellar vermis hypoplasia
   - **O**ligopherenia
   - Congenital **A**taxia,
   - **C**oloboma
   - **H**epatic fibrosis
6. Treatment: Control bleeding – band ligation / endoscopic sclerotherapy

CIRRHOSIS

- End result of destructive processes, producing fibrosis, scarring, and hepato cellular damage → leading to formation of nodules with distortion of hepatic vasculature and biliary system
- Nodule <3mm micronodular; >3mm – macronodular
- Distortion of vascular bed leads to portal HT and portal systemic shunting

Causes of childhood cirrhosis

- **Biliary cirrhosis – due to bile duct obstruction**
  - Biliary atresia or hypoplasia
  - Choledochal cyst
  - Cystic fibrosis
  - Bile duct stenosis or obstruction
  - Ascending cholangitis
- **Post necrotic cirrhosis – due to hepatocellular lesion**
  - Post hepatitis
    - Neonatal
    - Viral
    - Chronic
    - Drugs, toxins, poisons
  - Venous congestions
    - Constrictive pericarditis
    - CCF
    - Budd Chiari syndrome
    - Veno-occlusive disease
- **Genetic causes**
  - Wilsons dx
  - Galactosaemia
  - Alpha 1 antitrypsin def
  - Glycogen storage dx

Clinical features

- Palmer erythema, splenomegaly, heamorrhoids, cutaneous excoriations (pruritis)
- Large hard liver (biliary cirrhosis), small scarred liver (post necrotic necrosis)

Complications of cirrhosis

- Portal HT, variceal bleeding and hypersplenism
- Ascites, liver failure, encephalopathy
- Hepatorenal failure – rarely heaptocellular carcinoma

CHILD WITH PORTAL HYPERTENSION

EXTRA HEPATIC:
Portal vein thrombosis, umbilical vein sepsis, compression of portal vein by tumours/nodes, A-V fistula in portal system

HEPATIC

Pre-sinusoidal	Sinusoidal	Post sinusoidal
1. Congenital hepatic fibrosis • Firm liver especially left lobe • Polycystic kidneys • Portal HT 2. Wilsons dx 3. Sarcoidosis 4. Infiltrative dx 5. Myeloproliferation 6. Bilharzia	**CAH** (chronic active hepatitis) **Cirrhosis** Irreversible distorted hepatic vasculature and biliary system with nodules and hepatocellular damage. **Complications of cirrhosis** portal HT, hyperslenism, liver failure, hepatorenal failure **Complications of PHT** 1. Biliary malformation 2. Large hard liver 3. Galactosaemia 4. CAH 5. Haemachromatosis 6. Langerhans cell histioctytosis 7. Post necrotic →small scarred liver	• **Hepatic vein thrombosis** 1. Budd Chiari: Associated with heamoatol abn, cong defic antithrombin III, Behcets (uveitis, oral and genital ulcers). 2. Tumors (intrahepatic, IVC, leukemia), Congenital webs, Irradiation, GVHD, Liver abscess All these give acute obstruction of hepatic vein, IVC and tributaries. <u>2 types of Budd Chiari</u> **Oriental:** Characterised by webs, thrombosis and obstruction. Varying severity Chronic – not life threatening. Dilate veins **West type:** Acute iatrogenic tumour. Improves spontaneously. Death if not treated immed. Thrombolytic therapy, transplant • **Veno occlusive dx:** Insiduos onset obliteration of small hepatic veins. Mild histologic changes or severe with jaundice, hep failure DD: Cong CMO, constric peric. TB peritonitis, thoracic duct obstruction

HAEMATOLOGY

AN APPROACH TO ANAEMIA/PETECHIAE (W.Harris p262)

Approach (Achronym – SAND TEES – JACCOLST – SYSTEMS)

Scene: looking ill or well, look for clues around the bed
Looking ill: ALL, CRF, haemophilia, HIV infected, purpura due to meningococcemia

Anthropometry: draw up trangle of nutritional assessment

- Low weight → nutritional
- Low height with syndromes → SCA, CRF
- Increased OFC → subdural haematoma
- Small OFC → TORCH

Neurodevelopment

Dysmorphysm:

- Dyskeratosis congenita (male, leukoplakia, sparse hair, lacrimal duct stenosis)
- Wiskott-Aldrich (eczema, SOM)
- Fanconi (fanconi facies, microcephaly, small eyes, epicanthis folds, abnormal ears – shape, position, size – 10% MR). Short stature, growth failure, absent radii, hypoplastic supernumary bifid or absent thumbs
- Blackfan-Diamond (web neck, occular abnormality, cleft palate, bone deformity, triphalangeal thumb)
- Swachman Diamond
- Thrombocytopenia with absent radius (but thumbs present)
- Bossing (haemophilia, SCA)

Tanner staging: delayed in thalassaemia, SCA

Eyes: squint, ptosis, nystagmus (Fanconi, 6th nerve palsy with IC bleed)

ENT:

- Ear discharge, eczema, (Wiskott-Addrich)
- Evidence of epistaxis, angular stomatitis (IDA)
- Tonsills: hypertrophied → ALL, AML. Exudate → EBV

Skin:

- Hyperpigmentation of trunk, neck, interdiginous areas, café-a-late spots, vitiligo (Fanconi)
- Petechiae, purpura, echimosis → thrombocytopenia, vasculitis, aplastic anaemia
- Spider tallangiectasia, palmer erythema, spider nevi (chronic liver dx)

GPE (JACCOLST)

- Jaundice – haemolysis
- Anaemia – see palmer pallor
- Clubbing – CLD
- Cynosis – congenital HD
- Oedema
- Lymphadenopathy
- Splinter haemorrhages (SBE)
- Thyroid goiter (hypothyroidism)

SYSTEMS

Musculoskeletal/joints

Congenital dislocation of hips → Barlow, Ortolani tests
Swelling → haemophilia, JIA, SCA, HSP, ALL, IBD, Crohn's dx
Skeletal tenderness – ALL, NAI
Gait – posterior iliac crest – BM aspiration

GIT/Abdomen

Abdominal distension → chronic liver dx
Hepatospleenomegaly
Enlarged kidneys
Genitalia

- Males: small penis, undescendent atrophic or absent testes, hypospadias, phimosis
- Females: Malformed vagina, uterus and ovary
- Both sexes: Fanconi

CVS:

CCF, CHD associated bruising/syndrome
Cardiomyopathy – transfusion haemosiderosis with tjalassemia or SCA
Low BP: cardiomyopathy
High BP: HUS, CRF, microangiopathic haemolytic anaemia

CNS

Signs of increased ICP
Gait: hemiplegia, SCA – cerebral sickling, haemophylia, IC bleeding

INVESTIGATIONS

Urine analysis:
Blood: haemophilia, SCA, HUS
Hb: IV haemolysis
Protein, specific gravity: renal dx
Stool: blood → IBD, HSP
Temperature chart, fundoscopy
Blood: FBC → MCV & HbF – Fanconi
Ultrasound: absent /horse shoe kidneys

FANCONI'S ANAEMIA

- AR
- Presentation may have
    - Typical physical anomalies but normal haematological findings
    - Normal physical features but abnormal haematological findings
    - Physical anomalies + abnormal haematological findings → classic phenotype (39% cases)

Age at presentation
- 3-14 yrs
- Mean age 8-9 yrs
- Range 0-48 yrs

Pathology
- Abnormal chromosome fragility seen in metaphase preparations of peripheral blood lymphocytes cultured with phytohaemagglutinatinin and enhanced by adding clastogenic agents i.e. di epoxybutane (DEB)
- Cell fusion of Fanconi cells with normal cells or with cells from unrelated pts with Fanconi anaemia produces a corrective effect on chromosomal fragility – a process called complementation
- Tweleve complememtation groups are identified which led to cloning of 11 mutant Fanconi (FANC) genes
- Mutant gene proteins lead to genomic instability, chromosome fragility and Fanconi's anaemia
- Inability of Fanconi cell to remove oxygen free radicals → oxidative damage
- Leucocyte telomeric length is shortened & telomeric activity is increased → high proliferation in bone marrow → premature senescence → increased marrow cell apoptosis → increased TNF alpha & reduced interleukin 6 production

Laboratory finding
- FBC with diff: thrombocytopenia, then granulocytopenia, then macrocytic anaemia (over period of months to yrs)
- Marrow becomes progressively fatty similar to sever acquired aplastic anaemia
- Skin fibroblasts → chromosome fragility is enhanced when DEB is added
- Rapid screening diagnostic test: increased serum alpha fetoprotein levels
- Antenatal: abnormal chromosome breakage can be tested on amniotic fluid cells or with chorionic villus biopsy

Complications
- Frequent solid tumours
- Carcinoma of head, neck, upper esophagus, vulva, anus
- Oral cancer following bone marrow transplant
- 15% pts with Fancini may have acute leukaemia, or mylodysplastic syndrome

Treatment
- MDA
- If haematologic findings are normal → observation & subspeciality consultation can be arranged
- If growth velocity reduced than expect → GH def or hypothyroidism
- Screen for glucose intolerance / hyperinsulinaemia → annually or biannually
- Cancer screen annually
- Stem cell transplant is the only corrective therapy
- Recombinant growth factor therapy (RGFT)
    - GCSF x OD or every 2 days SC plus
    - Erythropoiten SC or IVI x 3 / wk
        - Results in increased neutrophil count
        - Sustained increase in plts & Hb aprox in 1/3rd of pts
        - But most loose response after 1yr due to progression of marrow failure
- Prognosis: projected median survival > 30 yrs

SHWACHMAN-DIAMOND SYNDROME

- AR
- Criteria (essential)
    - Exocrine pancreatic insufficiency
    - Cytopenias – variable due to BM failure
    - Normal chromosomes – no breakage after DEB clastogenic stress testing

Clinical features
- Fat malabsorption (50% cases)
- Short stature
- Neutropenias → fungal/bacterial infections
- Delayed bone maturation metaphyseal dysplasia short or flared ribs
- Thoracic dystrophy
- Bifid thumb
- Dental abnormalities (for oral hygein)
- Neuro-cognitive problems
- Poor social skills

Laboratory diagnosis:
- FBC: pancytopenia, neutropenia or abnormal neutrophils → aplastic anaemia
- BM Bx → marrow hypoplasia + fat infiltration
- CT/US: fatty pancreatic replacement
- 24 hr faecal fat
- Pancreatic function studies
- B cell / T cell/ Ig deficiencies

DD: Pearson syndrome

Complication: acute leukaemia

Important questations

What are the warning signs of primary immune deficiency?

1. Eight or more new ear infections within 1 yr
2. Two or more serious sinus infections within 1 yr
3. Two or more months on antibiotics with little effect
4. Two or more pneumonia within 1 yr
5. Failure of an infant to gain weight or grow normaly
6. Recurrent deep skin or organ abscesses
7. Peristant thrush in mouth or elsewhere on skin after age 1
8. Need for intravenous antibiotics to clear infections
9. Two or more deep seated infections
10. A family hx of primary immune deficiency

What are the grades of neutropenia?

Grad 1: $\geq$1.5 to 2.0 x 10^9 cells/L
Grad 2: $\geq$1.0 to >1.5 x 10^9 cells/L
Grad 3: $\geq$0.5 to ,1.0 x 10^9 cells/L
Grad: 4 <0.5 x 10^9 cells/L
(Ref: national cancer institute)

What are hyper-coagulable states?

1. Antithrombine III def
2. Protein S & C def
3. Factor V Leiden or prothrombin mutations
4. Proximal nocturnal haemglobinaemia
5. Pregnancy
6. Oral contraceptives

What are signs of iron overload?

1. Myocardium – cardiomyopathy – do regular echo
2. Pancreas – diabetes – glycosuria
3. Liver – cirrhosis – LFTs
4. Thyroid – TFTs for hypothyroidism
5. Pituitary – short stature, delayed puberty – GH

How would you treat iron overload?

1. Desferal – start at 5-6 yrs sc infusion
2. Give regular vitamin C – it enhances urinary excretion

AN APPROACH TO ABDOMINAL MASS

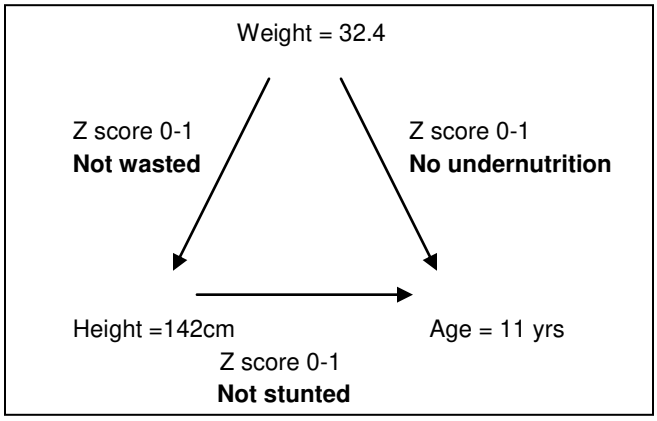
(Mock FCP on 24.09.2011 B3E)

History: 11 years old child presented with 1 year hx of abdominal distension

Approach (Achronym – SAND TEES – JACCOLST – SYSTEMS)

1. Scene:
Sitting comfortable with IV line at left forearm, running 5% dextrose with bicarbonate + bandage at left iliac crest – most lokely post bone marrow biopsy

2. Anthropometry (draw nutritional triangle and enter values and and then plot)



OFC: 53 cm (Z score 0-1) = normal
MUAC: 18 cm = normal (according to IMCI guideline)
Assess: no apparent mico/macro nutrient deficeincy noted

3. Neurodevelopmental assessment
- Vision and hearing – N
- Gross motor: upstaires / down staires
- Fine motor: able to copy complex diagrams
- Intellegence: 2 digit multiplication – no divisions
  - Knows address and details of family members
  - Writes 3 words sentence
  - Knows complex meanings
  - Knows name of president of country
- Speech: produce all speech sounds – including s, z, ng
- Social: takes full responsibility for personal care

Assess: appropriate for his age of 11 years old child

4. Dysmorphysm
No dysmorphism – I specifically looked for features of Beckwih Weidemman, Dany Drash and Wager complex

5. Tanner stage
Prepubertal – I specifically looked for Gonadal dysgenesis / DSD

6. Eyes
No periorbital ecchymosis or proptosis. Iris normal, no lid traction
No features of Horner's syndrome. N exam

7. ENT
No tonsillar hypertrophy, no wet patch on mucous membranes. N examin

8. Skin
Café a lait spots x 1 = 5 mm sq. Biopsy scar left inguinal region, bandage left iliac crest – like I said possible BM Bx. No patechiae, bruising or purpura, no axillary frackling, no BCG scar, no hypersensitivity reactions like Mx, phylinctanular conjuctivitis or erythema nodosum

General physical examination (JACCOLST)

- **Temp**. 36.5 C = no fever
  [Fever + mass abdomen: hepatitis / mononucleosis / leptospirosis]
- No **Jaundice:** looked for chronic liver dx (CLD)
- No **Anaemia** (pallor) – if transfused – must be masked – anamia of chronic dx, haemolytic annaemia
- No **Clubbing** (CLD)
- No **Cyanosis** (CHD, CF)
- No **Oedema** (CLD)
- **Lymph nodes**: checked all groups – palpable 0.5 cm normal consistancy, non matetd, non tender, not attached with underlying tructures and no skin changes – normal LN
- No **Splinter haemorrhages**
- No **Thyroid** enlargement

Abdomen
Distended – no prominent veins or scar marks
Tender left iliac fossa - ?due to biopsy

Masses x 2
One on the right iliac fossa 3x4 cm tender on palpation, firm and mobile – not attached to the under lying structures
Second on the left iliac fossa 3x4 cm non tender on palpation frim and mobile – also not attached to the underlying structures
Was unable to palpate mesenteric / para aortic lymph nodes

Liver: 6 cm below costal margin at MCL: span 12 cm, firm, non tender, round edge, no pulsation / brui
Spleen: not palpable

No features suggestive of ascities – dullness / shifting dullness
Summ: hepatomegally with x 2 masses – no features of heart failure, chronic liver dx or portal hypertension

CVS
HR 90 / min, all pulses palpable and equal – normal rate, rhythm, volume and character. No radioradial or radiofem delay. BP 110/50 mm/Hg – normal (gets high in pheochromocytoma / neurohormonal tumors). Praecardium normal. Apex beat 5 ICS, MCL. Trachea central. HS normal. No murmur. No signs of CCF, RHD, SEBE or pleural effusion.

Chest
Normal shape. RR 20/min. Normal respiratory pattern. No scars, no tenderness, percussion note resonant. GAEB. I specically looked for features of possible lung metastasis. Nephroblastoma (usually encapsulated) spreads in lungs.
Summ: chest exam N

CNS
Fully conscious – no abnormal movement
No flapping tremors
No signs of mening irritation (Kern/Brodz)
No signs of increased ICP
Cranial nerves examined

- He fixes and follows
- No ophthalmoplegia
- No facial asymetry
- Hearing intact
- Tougue central
- Gag present
- No drooling :: no cranial nerve abn noted

Motor BPTR (bulk, power, tone, reflexes) bilateral, UL/LL, distal / proximal - normal
No cerebellar signs
Sensations intact
Spine normal
Summ: CNS examination - N

Musculoskeletal
Normal gait
No joint pains or tenderness or swelling
No limitation of movement
Summ: N exam

In summary

I am presenting SM, an 11 years old African male child who has presented with 1 yr hx of abdominal distension. He has N anthropometry and neurodevelopment. He has significant generalised LAD, grossly enlarged hepa and x 2 abdominal masses.

My DD of SM would be:

1. Disseminated TB: as evidenced by signs of LAD and haepatomegaly. However he doesn't have any apparent hypersensitivity reactions and has normal neurodevelopment and anthropometry.
2. Abdominal tumors: of which most likely is lymphoma as evidenced by palpable abdominal masses, bone marrow biopsy scar and alkalanising fluid running through IV line. Abdominal distension may be secondary to subacute gut obstruction or intusseption. Non Hodgkin's lymphoma of the bowel is uncommon
3. Neuroblastoma: as it is firm and irregular and extends across the midline. However it commonly occurs in young children. Usually encapsulated neuroblastoma spreads in lungs will look for cannon ball appearancce on CT chest.
4. Rhabdomyosarcoma / Lieomyosarcoma – are tumors if genitoutinary and GIT respectively.
5. I also thought of Wilms tumor – but masses are not arrising in renal areas and there are no features of HTN or varicocele
6. Omental & mesenteric cysts should also be considerd
7. Duplication/ Meckle's diverticulum are other diff diagnosis

My approach to this child would be first to ask for history of TB contact, HIV status of the child and use of any medications and blood transfusions followed by approprite investigations as follows:

First:
Would be the exclusion of TB by doing full TB screen
FBC, ESR, sputum AFB, Gene Xpert and CXR
FBC would also help to exclude bone marrow infiltration (anaemia, thrombocytopenia, neutropenia).

Second:
AXR – air fluid levels and calcifications (neuroblas / teratoma)

Third:
US abdomen → origin of abdominal masses – cystic / solid?

Fourth:
CT/MRI abdomen to delinate the masses and see extent and infilteration into adjacent organs. CT abdomen in TB may show enhancement of lymph nodes but steroid use may have masked this sign

Fifth:
U/E: Tumor lysis syndrome / renal involvement
Uric acid / lactate/ LDH → rapid cell turn over – associated with malignancies

Sixth:
Urine – chemistry and dipstix: lesions involving kidneys → loss of proteins and blood → Wilms / renal masses
Urine: homovallinic acid and vanillylmandelic acid → elevated levels are associated with neuroblastoma / pheochromocytoma

Seventh:
Examination of stool → malena or blood in stool

Eight
Serum beta hCG and alpha fetoproteins → can be used as tumor markers that can aid in the diagnosis and followup of teratomas / liver and germ cell tumors

Ninth
Bone marrow biopsy

Tenth
IVP to differentiate neuroblastoma from Wilms tumor if suspected

Eleventh
Radiological evaluation of chest and skeletal survey → metastatic spread of tumor
In females ovarian tumors (mass in the presence of hirsutism, tender breasts, virilization and clitoromegaly) suggest ovarian tumor with excessive hormonal production.

Management
- Acute management: depends upon initial investigations
- NPO if gut involment or possibility of intestinal obstruction
- NGT insertion and free drain if above is suspected
- Alkalinisation fluid to continue to prevent tumour lysis syndrome
- Allopurinol
- Close monitoring of vital signs
- IV antibiotics if suspected underline infection
- Parents counselling and psychologist referral
- Trace the bone marrow results as soon as spossible

NEUROLOGY

NEONATE WITH SEIZURES

Hypoglyceamia

- Low stores – IUGR, inadequate intake, prematurity
- Normal stores – abn metabolism
    - **Ketones** – tyrosineamia, galactoseamia, GSD and amino acid defects
    - **Non ketones** – fatty acid abn
- High insulin / increased glucose consumption (Pract Endo & Diab in child p 35)
    - Hyperinsulism
    - Transient neonatal hyperinsulism
    - Infant of diabetic mother
    - Insulinoma
    - Beckwith – Wiedemann syndrome
    - Rhesus haemolytic disease
    - Perinatal hypoxia
    - Malaria
- Hormonal deficiency
    - Hypopituitarism
    - Adrenal insufficiency
    - Hypothyroidism
    - Glucagon deficiency

Normoglycaemia

- Infection: meningitis, septiceamia
- Asphyxia: brain damage, IVH, SAH
- Hypothermia
- Vasculitis – SLE
- Trauma: child abuse
- Structural brain abn:
- Abnormal migration: Lissencephaly, porencephaly, hydrancephaly, schizencephaly
- Agenesis of carpus callosum
- Astrocytoma
- Myelinomeningocoele
- Neurocutaneous syndromes
    - NFib
    - Tub Sclerosis
    - S. Webber syndrome
    - Incon Pigmentosa
    - Ceroid lipofuscinosis
- AD/AR microceph
- Metabolic – Ca, Mg, BS

Investigations:

- BS, Urine – ketones, red substances
- ? Visceromegaly
- Low BS – insulin, cortisol
- Exclude infection / metabolic abn.
- May need liver bx
- CT/MRI abdomen,
- NBS – CT scan, LP

EPILEPSY (B Nelson p835)

1. Partial seizures – arise from specific anatomic focus
   - Simple partial seizures – consciousness preserved
   - Complex partial seizures – conscious impaired
2. Generalised
   - Tonic – producing and restoring normal tone
   - Clonic – pertaining to clonus (clonus – spasm in which regidity and relaxation succeed each other0
   - Tonic-clonic
     - Can lead to status epilepticus
     - Generalised tonic clonic activity lasting > 20 min
3. Absence seizures
   - 3H spike & wave activity
   - Provoked by hyperventilation – last for few seconds
   - Atypical absence seizures – manifest as episodes of impaired consciousness with automatism, autonomic and motor manifestations
   - Myoclonus – lightning like jerk of part of body / shock like contractions of te muscle or group of muscles – rapid rhythmic movements
4. Epileptic syndromes
   - Benign focal epilepsy – Rolandic
     - 5 – 10 yrs – during sleep / awakening
     - Focal motor – face / arms
   - Benign neonatal convulsions – AD, 3 day fits, or familial 5th day fits
   - Juvenile myoclonus epilepsy – AD, adolescents, morning myoclonus occuring predominently with in 90 minutes of awakening
   - Infentile spasms - (2-10 sec) – contraction of neck, trunk, and arm muscles followed by state of sustaiend muscular contraction
   - Lennox-Gastaut syndrome
   - Astatic-akinetic / or atonic seizures
   - Acquired epileptic aphasia (Landau-Kleffner syndrome)
   - Rasmussen encephalitis

5 YEAR CHILD OLD WITH SEIZURES

Differentiate seizures from shuddering attacks, hereditary chin trembling, and paroxysmal attacks: kinaesigenic chorea and pseudoseizures

CAUSES (B Nelson p837)

1. EPILEPSY
1. Juvenile ME – in adolescents
2. Typical ME of childhood
3. Rolandic – Benign focal epilepsy
4. Lennox Gastaut syndrome

2. INFECTION
1. Meningitis
2. Rasmussen encephailitis (6-10 yrs)
3. Pyrexia
4. Septiceamia
5. Typhoid

3. TRAUMA /POST TRAUMA / MALFORMATIONS
1. Gliosis – excessive development of neuroglia tissue (neuroglia is the supporting structure of the brain and spinal card)
2. Bleed medial temporal sclerosis
3. Hamartoma
4. Subarachnoid cyst
5. AV malformation → complex Partila seizure
6. HIE → complex myoclonic, epilepsy, CP

4. VASCULITIDES
SLE

5. STRUCTURAL BRAIN ABNORMALITY
1. Aicardi
2. Tuberous sclerosis
3. Sturg Webber syndrome
4. Klipple Trenaunay- Weber synd
5. Neurofibromatosis

6. DEGENERATIV DISEASE
1. Huntington's
2. Aaxia telngiectasia

7. MYOPATHIES
1. Progressive ME
2. MERRF
3. MELAS
4. Ceroid lipofuscinosis
5. Juvenile
6. Gauchers dx
7. Axonal dystrophy

8. METABOLIC ABN
1. Hypoglycaemia
2. Hypo Ca, Mg, Na
3. Hyper Na,
4. Storage dx
5. Reye syndrome
6. Degenerative disorder
7. Porphyria
8. Pyridoxin dependancy / deficiency

9. DRUG: over dose / withdrawl

INVESTIGATIONS
1. Metabolic screen incl U/E & BS
2. CT scan
3. EEG
4. Ms Bx
5. FBC -?infection

ABNORMAL MOVEMENTS IN A CHILD (Neuro Tutorial B3E)

Site: basal ganglia – extra pyramidal

- Voluntary
- Involuntary

Involuntary

- Rhythmic → seizures
- Non rhythmic
  - Chorea
    - High amplitude
    - Jerky
    - Pseudopurposeful
  - Sydenham's → jerk in the box → tongue

Differential diagnosis

Congenital

- Infections
- Hypoxia
- Genetic
  - Huntington's chorea – AD
    - Chorea
    - Hypotonia
    - Seizures
    - Dementia

Acquired

- Infections
  - Labrynthitis (vertigo, nystagmus, tinitis, hearing loss, N&V)
  - Ramsay Hunt syndrome – features of facial palsy
- Vascular
- Neoplasms of brain
- Autoimmune - SLE
- Post infectious (Rheumatic F)
  - Sydenham's chorea – St Vitus dance
    - Hyperkinetic movement disorder
    - Emotional lability
    - Hypotonia

Metabolic

- Drugs – toxins (bronchodilators, amphetamines, tricyclic antidep)
- Endocrine – hyperthyroidism / hypothyroidism / hypocalcaemia

Dystonia – sustained contraction of agonists and antagonists

- Generalised
- Focal
- Segmental
- Hemidystonic

MOVEMENT DISORDERS (B Nelson p852, Paed Neurology Weiner & Levitte p265)

1. Chorea
2. Athetosis
3. Dystonia
4. Tremors
5. Myoclonus
6. Tics

1. Chorea

Fidgity behavior, inability to sit still, clumsiness, dysarthria and awkward gait
Abnormalities may be:
Congenital - infections, hypoxia, familial
Acquired

- Metabolic
- Vascular
- Toxins & drugs
- Infectious
- Neoplastic

Or
As a part of more neurological disorder

- Sydenham's chorea – post infectious (RF)
- Huntington's chorea
- Cerebral palsy
- Reaction to drugs or toxins

2. Athetosis

May occur in combination with chorea – all above may cause athetosis
But most prominent cause is encephalopathy
Athetosis is aprominent feature of:

- **Ataxia telangiectasia**
  - Age 1-2 yrs
  - Progressive ataxia, dystonia, chorea, swallowing difficulty, poor facial movements , oculomotor apraexia
  - Intellent is preserved
  - Conjunctival telangiectasia → age of 5 yrs, prematurily grey hair, atrophic skin changes
  - Daignosis (increased alpha fetoproteins, decreased IgA and circulating T cell levels, Westrn blot – ATM protein)
- Degenerative conditions like
  - **Hallervorden-Spatz dx**
    - Degeneration of basal ganglia
    - Deposition of Fe in damaged tissues - Fe metabolism normal
    - Progressive dystonia, pigmentary degeneration of retine, acanthosis rigidity, spasticity, dementia – no therapy

- **Friedrich's ataxia**
  - AR – manifest in early teenage yrs.
  - Ataxia, dysmetria, dysarthria,
  - Pes cavus, hamme toes, diminished prioprioception and vobration
  - Diminished / absent reflexes
  - Upgoing toes
  - Kyphoscoliosis
  - Nystagmua
  - Hypertrophic cardiomyopathy
- Wilsons dx
- Kernictarus (choreoathetosis)

- Metabolic
  - Palizaeus-Merzbacher dystrophy
  - Abetalipoproteinaemia
  - Lesh Nyhan
  - Thyrotoxicosis
  - PKU

3. Dystonia (Paeds Neuro p261)

An abnormal attitude of posture that results from co contraction of agonist & antagonist muscles

Causes:

- Drugs – phenothiazines, dopamaine receptor blockers
- Hysteria – paroxysmal onset – improves with assurence
- Symptomatic – post infectious, collagen vascular
- Traumatic
- Toxin – CO
- Post infarction
- Congenital / genetic dystonia, dystonic CP
- Metaboolic – Wilsons, Huntingtons dx

4. Tremors

Rhythmic, oscillating movements with a predictable speed, amplitude and force

Tremors may be slow or rapid

- Psychologic
- Cerebellar origin
- Thyrotoxicosis
- Hypoglycaemia
- Wilson's dx
- Drugs
  - Bronchodilators
  - Amphetamines
  - Tricyclic antidep

5. Myoclonus

Rapid jerking of muscle or group of muscles, usually with displacement of a joint
Mostly myoclonus is attenuated by sleep & is seen as manifectation of:

- Various epilepsies
- Infections
- Toxic encephalopathies
- Metaboolic encephalopathies

6. Tics

Sudden stereotypic movements that can be either motor or vocal
They are involuntary and with effort & can be supressed
Unlike chorea they are readily reproducible by the patient and the observer
Clinical characteristics:

- Increase with stess
- Usually not seen in sleep
- Usually proximal or oral buccal
- Benign in the last half of the first decade of life or may be lifelong
- Types: simple, vocal or complex

UNSTEADY GAIT – ANATOMICAL CLASSIFICATION

1. Muscle diseases
- Myopathy
- Muscular dystrophy
- Myesthenia gravis
- Myotonic dystrophy

2. Infections / post infectious
- Echo / EBV/ Herpes (acute cerebellar ataxia)
- CSF: lymphocytes pleocytosis
- 30% have residual damage - recovery in days, weeks or months

4. Drugs / toxins
- Phenytoin
- INH
- Haloperidol
- Pb / Hg

5. Metabolic disease
- Mc Ardles
- Maple syrup urine
- Hartnup
- Ablipoproteineamia
- Refsums

6. Bony abnormality
- CDH

7. Spinal abnormality
- Congenital – spina bifida
- Post traumatic
- Post infectious – TB spine

8. Neuropathy
- Sensory ataxia - lesion in posterior columns of spinal cord / dorsal roots / peripheral nerves, impaired joint position sense and positive Romberg
- Hereditary
- Acquired

9. Central abnormality
- Hemispheric damage:
  - Dystaxia of volitional movement - past pointing, overshooting
  - Dystaxia of eye moevemnt - opsoclonus, nystagmus, occular flutter
- Cerebellar disease
  - Damage to vermis – gait / truncal ataxia, head titubation and rebound phenomeneon
- Degenerative diseases

CHILD WITH TOE WALKING

Child walks on toes without putting much weight on the heel or other parts of the foot

- Common in toddlers
- They usually adopt a normal walking pattern as they grow older
- If problem exists past the age of three, the child should be evaluated

Factors causing toe walking:

- Habitual" or "idiopathic" toe walking - cause is unknown
- Prolonged walking ring exposure
- Congenital short Achilles tendon
- Muscle spasticity - especially when associated with cerebral palsy
- Paralytic muscle disease such as Duchenne muscular dystrophy
- Early sign of neurodevelopmental and communication disorder
- Autism - toe walking may be due to a dysfunctional vestibular system

Diagnosis:

- Evaluate whether there is unilateral or bilateral toe walking
- Evaluate range of motion
- Perform a basic neurological examination

Treatment:

- Idiopathic (in young children) – watch and wait – child may outgrow
- If reduction in child's range of movements go for other options:
    1. Wearing a brace or splint either during the day, night or both – it limits the ability of the child to walk on his or her toes and stretches the Achilles tendon. Commony used brace is an AFO (ankle-foot orthosis).
    2. Serial casting - the cast is changed weekly with progressive stretching
    3. Botulinum toxin (Botox therapy) to paralyze the calf muscles to reduce the opposition of the muscles to Achilles stretching, usually together with serial casting or splinting
    4. If conservative measures fail after about 12–24 months, surgical lengthening of the tendon is recommended. After the surgery, a below-the-knee walking cast is worn for six weeks and then an AFO is worn to protect the tendon for several months
    5. For toe walking which results from more serious neuro-muscular conditions, additional specialists may need to be consulted.

SHORT NOTES

Myopathy

1. Central core disease
    - Floppy with proximal weakness
    - Pathology – centrally placed cores of degenerative myofibrils in type 1 fiber
2. Congenital fiber type
    - Floppy
    - Joint contracture
    - Hip dislocations or arthrogryposis
3. Myotubular
    - Proximal weakness
    - Respiratory difficulties
4. Nemaline (rod body) myopathy
    - Proximal weakness
    - Floppy
    - Myopathic facies – long and narrow
    - Club feet / kyphoscoliosis

Dystrophy – progressive distruction of muscles

1. Congenital muscular dystrophy – present at birth or soon after birth
2. Fukuyama type C and D
    - Weakness – proximal or distal
    - Mental retardation / microcephaly
    - Contractures
3. Duchenne (2-4 yrs) & Becker type (late childhood and adolescents)

Myotonic dystrophy – congenital myotonic

- Respiratory and feeding difficulties at birth
- Inverted V or tenetd T signs (inability to proximate lip closure)
- TEV
- Improvement of strength overtime / 50% retarded
- Myotonia not present at birth – develop early to late childhood
- Predisposition to malignant hyperthermia with anaesthesia

Friedrich's ataxia – AR – manifest in early teenage years (GAA expansion)

- Ataxia
- Dysmetria / dysarthria
- Pes cavis / hammer toes / upgoing toes
- Diminished proprioception and vibration / absent reflexes
- Kyphosis
- Nystagmus
- Hypertrophic cardiomyopathy

CLASSIFICATION ACCORDING TO THE TYPE OF ATAXIA

(B Nelson p850, Forfar p966, Ziai p92)

Acute ataxia

1. Drugs
   - Phenytoin
   - INH
   - Haloperidol
   - Pb
   - Hg
2. Infections/ post infectious
   - Echo / EBV/ Herpes (acute cerebellar ataxia) – CSF lymphocytes pleocytosis, 30% have residual damage - recovery in days, weeks or months
3. Tumours
   - Meduloblastoma
   - Ependymoma
   - Cerebellar astrocytoma
4. Peripheral neuropathy
   - Miller – Fischer variant of GBS
5. Vasculitis
   - TB
   - SLE
   - HSP
6. Inflammatory diseases: infections
   - Encephalitis
   - Brain stem encephalitis
   - Meningitis
7. Heamorrhage & stroke
8. Hydrocephalus with increased ICP
9. Acute labrynthitis
10. Traumatic brain injury
11. Multiple sclerosis
    - CSF pleocytosis with normal / high globulin
    - Onset age 15 yrs
    - Multifocal demylination with perivascular infilterates
    - Guarded prognosis

Acute intermittent

1. Maple syrup urine disease
2. Hartnup disease
3. Abetalipoproteinaemia
4. Vitamin E deficiency
5. Leigh disease
6. Wilson's disease
7. Organic acidemias
8. Refsum disease
9. Metachromatic leukodystrophy
10. Krabbes disease

Chronic progressive

1. Post fossa tumours
    - Gliomas
    - Astrocytoma
    - Ependymoma
    - Meduloblastoma
2. Degenerative disease,
    - Friedriech ataxia
    - Ataxia telengiectasia
    - Pelizaeus- Merzbacher disease
    - Ramsay Hunt syndrome

Chronic non progressive

1. Arnold Chiari
2. Dandy Walker – classic
3. Jobert
4. Angelman
5. Ataxic cerebral palsy

2. Congenital cerebellar abnormalities

FLOPPY INFANT (Paeds Neuro p44)

GENERAL HISTORY & EXAMINATION

- **Family history of:**
  - Myotonic dystrophy
    - Shake hand with mum
    - Look at parents faces
    - Close hand and open quickly
  - SMA
  - Siblings
  - Chromosomal disorders
- **Preganancy and delivery:**
  - Viral infection- TORCH
  - Hydramnios in myotonic dystrophy
  - Decreased foetal movements
  - Traumatic delivery (intraspinal, intracranial, peripheral nerve dysfunction)
  - Need for resuscitation
  - Apgars
  - Premature
  - Poor cry
  - Poor suck
- Sedation to mum
- Neonatal hypoglycaemia
- Milestones

SPECIFIC EXAMINATION

1. Floppiness:
   - Frog like position
   - Head lag
   - Ventral suspension
   - Check movements around each joint
   - Check tone when held under armpit
   - Check reflexes
     - Reflexes brisk → CP.
     - Normal/absent → SMA.
     - Persistence of primitive → HIE / CP
2. Alert/dull
3. Chest – signs of respiratory infections / aspiration
4. Movements, sucking, feeding, paradoxical movements
5. Weakeness or no weakness - proximal or distal weakness
6. Facial features – syndromic, myopathic, rash, opthalmoplegia
7. Fasciculation esp tongue, hypoglossal nerve, also hands, abdominal muscles
8. Joints examination
9. CVS examination

CAUSES

Hypotonia without weakness

HISTORY

1. Hypotonic CP
2. Perinatal history
    i. Movements in utero
    ii. Polyhydramnios
    iii. Difficult delivery
3. Milestones
4. Hearing
5. Vision

DYSMORPHYSM

1. **Downs** – look for features of DS
2. **Zellweger's** – Cerebro-Hepato-Renal syndrome
    - AR degenerative dx affecting brain, kidneys and liver
    - Severe hypotonia with large fontanelles and high forehead
    - Hepatomegaly
    - Redundant skin folds of neck are characteristic
    - Death <1 yr
    - Biochemical defect of Peroxisomes
    - Decreased ability to synthesise various phospholipids
3. **Pradar Willi**
    - Hypomentia
    - Hypogonadism
    - Hypotonia with feeding difficulties
    - Obesity
4. **Lowes –** Occulo-Cerebro-Renal
    - X linked recessive
    - O →cataracts glaucoma, bupthalmos, leading to severe visual impairment
    - C →severe hypotonia, inecreased reflexes and mental retardation
    - R → Fanconi's syndrome , organic aciduria
5. **Menkes Kinky Hair**
    - Disorder of copper metabolism dominated by neurodegenerative symptoms and connective tissue disturbances
    - GR
    - Cerebellar degeneration
    - Sever vasculopathy
    - Fractures

CONNECTIVE TISSUE DISORDERS

1. **Cutis laxa:** AR/AD
   - May be congenital or acquired
   - Can occur following febrile illness / drug therapy
   - Child looks prematurely age - skin hangs in pedulous folds
   - Cheracteristic facial features → age appearance with sagging jaws, hooked nose, everted nostrils, short columella, long upper lip and everted lower lip
   - No hyper elasticity and hypermobility of joints
2. **Erhlos Danlos:**
   - Normal at birth – followed by hyperelasticity, fragility and bruisability of skin
   - Confused with cutis laxa - due to defect of collagen
   - No specific treatment
   - Life expectancy usually normal
   - Orthopeadic management
   - Correct bleeding/vascular anomalies
3. **Osteogenesis imperfecta:**
   - Type I – AD. Blue sclera. Excessive fragility and conductive hearing loss.
   - Type II – AR. Lethal
   - TypeIII – Blue sclera which becomes normal. Die in infancy. Very short stature
   - Type IV – AD. Short stature
4. **Marfans:** Look for features of Marfans Syndrome

INBORN ERRORS OF METABOLISM OR TORCH INFECTIONS

- Organic Acidaemia: Starvation ketosis, ketotic hypoglyceamia, lactic acidosis
- Carnitine deficiency: Increased ketones, low blood sugar, lethargy, muscle weakness and CMO. Note increased anion gap
- TORCH infections: look for specific signs as per suspected infection
- General considerations in all inborn errors
  - Family history
  - FTT
  - Chemical clues:
    - Ammonia increased,
    - Hypoglycaemia
    - Acidosis
    - Ketonuria
    - Abnormal hepatic transaminases
    - Jaundice

METABOLIC

- Rickets
- Hypercalcaemia
- Hypothyroidism

BENIGN CONGENITAL HYPOTONIA (B Nelson p 848)

Manifests at 6-12 months of age – present with delayed gross motor skills – child unable to sit, crawl, and creep but good verbal and social skills, intellegence and appearance

Hypotonia with weakness

1. Spinal cord

- Transverse myelitis: presents early as spinal shock with sensory level
- Spinal cord trauma
- Spinal cord tumour – infarction, demylination
- Spina bifida
- Syringomyelia

2. Anterior horn cell

- SMA
- Polio
- Other viral infections – coxsackie, echo

3. Peripheral neuropathies

- GBS – symmetrical flaccid paralysis, areflexia
- Infectious – post-diptheritic , Lime disease
- Charcot Marie Tooth
- Toxins – lead
- Drugs – vincristine, INH
- Nutritional – vitamin B6, B12, E defiency
- Metabolic – diabetes, Refsums, uraemia

4. Neuromuscular junction

- Myasthemia gravis: transient, congenital , acquired
- Botulism: presynaptic
- Tick paralysis
- Organophosphates

5. Muscle

1. **Congenital myopathy**
   - Central core dx
   - Nemaline rod dx (rod body)
   - Myotubular dx (foetal)
   - Fingerprint
   - Congenital fibre type disproportion

2. **Metabolic**
   - Mitochondrial myopathy
   - Glycogen myopathy
   - Glycogen storage dx
   - Lipid storage dx

- Periodic paralysis – hyperkalaemia, hypokalaemia (fluctuating weakness)
- Proximal muscle weakness
    - Cushings syndrome
    - Hypothyridism
    - Hyperthyroidism
    - Hyperparathyroidism

3. Dystrophies

- Congenital muscular dystrophy
- Myotonic dystrophy
- Duchennes/Becker
- Limb girdle
- Fascio-scapulo-humural

IMPORTANT SIGNS ASSOCIATED WITH CLINICAL CONDITIONS

1. **Hypotonia with sucking and swallowing difficulties in newborn** – think of :
    - SMA
    - Congenital muscular dystrophy
    - Prader Willi
    - Neonatal myasthenia gravia
    - Birth trauma

2. **Facial weakness**
    - Myotonic dystrophy
    - Myotubular dystrophy
    - Mysthenia gravis
    - Congenital muscular dystrophy
    - Africa SMA

3. **External opthalmoplegia**
    - Myotubular congenital myopathy
    - Mysthenia gravis
    - Mitochondrial myopathy
    - Congenital dystrophy myotonia

4. **With arthrogryposis**
    - Neuromuscular dx
    - IU factors
    - Congenital muscular dystrophy
    - Congenital myotonic dystrophy
    - Denervation syndromes

INVESTIGATIONS IN A FLOPPY CHILD (B Nelson p847)

Guided by clinical ecxamination

- **CK**
  - Increased in all infants in 1st 7 days of life
  - Increased in DMD, BMD, dermatomyositis, and polymyositis
  - Mildly increased or normal in congenital myopathies
  - Increased in hypothyroidism
  - Normal in SMA
- **Nerve conduction:**
  - Slow in peripheral neuropathy - normal in SMA.
  - Decreased in demyelination neuropathies e.g MLD, Krabbes, Leighs
- **EMG:** SMA – fibrillation potential. Polio – denervation
- **Muscle biopsy:** SMA – group atrophy
- **ECG:** SMA – base line fibrillation, Pompes, CMO
- **Chromosomes** – if indicated, DNA analysis
- **Metabolic screen:** U/E, lactate, pyruvate, glucose, LDH, ammonia
- **Ca, PO4, Mg** (rickets, hypocalcaemia)
- **Drug levels** – if indicated
- **LFTs** – Billirubin
- **TFTs**
- **FBC**, Diff, ESR
- **Tensilon test** (neostigmine), acetylecholine receptor antibodies
- **Botulin toxin**
- **Cyanide nitropriside test**
- **Vitamin** E, B6, B12 levels
- **CXR**
- **Stool:** botulism culture and toxin, compylobactor culture
- **CSF** – protein, cells
- **MRI** of spinal cord or brain (if micro/macrocephalic)
- **Urine** metabolic screen, organic acids

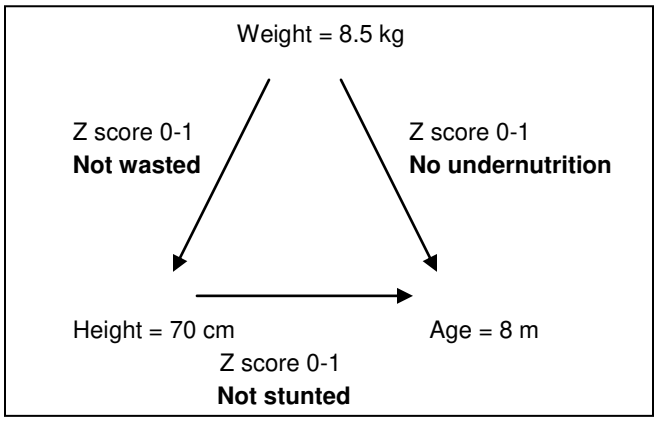
MOCK FCP: CASE PRESENTATION B1E

History

Andile, 8 months old male child, unable to sit without support and suffrering from recurent chest infestions since birth

Approach (Achronym – SAND TEES – JACCOLST- Systems)

1. **Scene:** Lying in mothers lap with IV line at right arm running PMS at 5 ml /hr
2. **Anthropometry** (draw up nutritional triangle and enter values and and then plot)



OFC: 40 cm (Z score -3) = microcephaly
MUAC: 13 cm = normal (according to IMCI guideline)
Assess: Microcephalic → indication of chronic disease or chronic malnutrition.
No apparent micro nutrient deficeincy noted

3. **Neurodevelopmental assessment**
   - Reduced vision but hearing seems N
   - Gross motor: no rolling over, head lag present, unable to sit, no weight bearing, fisting, pimitive reflexes as follows:

Primitive Reflex	Andile	Primitive reflexes of normal infant
Moro	Present	Disappears @ 4-5m
Tonic neck	Present	Seen at 2 -3 weeks, disappears @ 1yr. Persistance of it predicts development of choreoatheetotic CP
Cross adductor	Present	Disappears @ 7-8m
Ankle clonus	Absent	Disappears at 2-3m
Babinski	Absent	May persist till 1 yr untill weight bearing
Grasp reflex	Present	Disappears @ 4-5m (even at birth hands should be open for 50% of the time. If hands do not open by 3m → pyramidal dysfunction
Placing and stepping	Present	Elicited by stroking dorsal surface of feet on table. Present @ birth till 1yr or until child bears wt.
Parachute reflex	Asymetric	Develops @ 6-7m – good sign of upper extremity motor development. If assymetric → early sign of pyramidal disease
Landau response	Absent	Appears @ 4 m
Hand use	Does not transfer	Hand use @ 4-5m – grasp and reaching for objects and transferring @ 7-8m

- Fine motor: holds rattle, does not reach out, does not transfer
- Intellegence: looks around,
- Speech: babbles, coos, chuckles, don't respond to name
- Social: no stranger anxiety
- **Assess:** Neurodevelopmentally assessed as 3 months old infant

Exam question: two reliable signs that infant is developing with normal intellegance are: 1. Early onset of pincer grip (9-15m) 2. Early acquisition of language (1yr)

4. Dysmorphysm: No dysmorphysm

5. Tanner stage: Infant – did this for completeness of exam

6. Eyes: Red reflex is not present→ cataract bil. No corneal cloudiness (MPS). Intra occular pressure seems normal. No squint. Would like to do fundoscopy especially for disc oedema to rule out cranial tumors → retinoblastoma

7. ENT: Pinna & external auditory meatus N. Tongue of normal size. Tongue fasciculations not present →SMA.

8. Skin: Café a lait spots x 2 = 5 mm sq on the trunk. No patechiae, bruising or purpura. No axillary freckling.
No BCG scar and no Mx.
No vasicular rash: Herpes → Bells. Varicella Zoster → Ramsay Hunt
No dryness of skin → hypothyroidism.
Hair not blond or kinky → Menkes

9. General physical examination

N temp, no jaundice, no cyanosis, maintaining airway (JACCOLST – normal)

10. CNS

Posture → frog like
Fontanelle → normotensive (if buldging → increased ICP, SOL)
Breast feeding (if poor feeding → bulber palsy)
No high pitched cry (if present → cerebral dysfunction)
Fully conscious – No signs of meningitis
Spine normal (no spina bifida → MMC)
Manoeuvers:

- Infant placed prone → unable to extend upper limbs
- Lower limbs exam:
  - Normal joint mobility
  - No contracures
  - No joint dislocation
  - Reduced strength of withdrawl
- Reflexs – all limbs pathologically brisk with positive cross adductor but no Babinski

11. CVS:

No signs of CCF (Bacterial/Infective endocarditis). No cadiomegaly (Pompe disease)
No cranial or renal brui (vein of Gallon, arteriovenous malformation)

12. Respiratory:

Normal breathing pattern (neuromuscular disease if abnormal breathing). Grade 1 strider, bilateral coarse crackels, bronchial breathing at right middle zone and occasional wheez. No dullness on percussison.

13. GIT:

No hepato spleenomegayy (storage diseases)
Normal genitalia
Anus patent – not patulous
Bladder not palpable

14. Summary:

I am presenting 8 months old infant who has normal weight for age and is not stunted or wasted but has microcepahy. He seams to have reduced vision secondary to bilateral cataracts and functioning at the age of 3 months old infant. His CNS examination reveals that he is floppy without weakness as evidenced by his frog like posture, persistence of primitive reflexes and other signs of UMNL. Andile has also severe pneumoinia / lobar pneumonia as evidenced by tachypnoea, coarse crackles bronchial breathing.

In order to make differentia diagnosis of Andile a detailed perinatal history (in-utero movements, polyhydramnios, and difficult delivary), milestones and hearing and vision assessment will be required.

In the light of current information & clinical examination my DD of Andile will be as follows:

- TORCH infectrions – most likely Rubella (microcephaly, bilateral cataracts, signs of UMNL)
- Inborn errors of metabolism – amino acid, fatty acid or carbohydrate metabolism (but Andile has no organomegaly)
- HIE (perinatal insults – detailed history of preveious admissions in nursery etc is required)
- HIV encephalopathy (need to know the status)
- Genetic cause / syndrome (no dysmorphism noted)
- Connective tissue disorders – unlikely

15. Investigations

- **Metabolic screen:** U/E, lactate, pyruvate, glucose, LDH, ammonia
- **Ca, PO_4, Mg** (rickets, hypocalcaemia)
- **Plasma glucose**
- **LFTs** – Billirubin
- **TFTs**
- **FBC**, Diff, ESR, CRP (current pneumonia)
- **CXR**
- **Mantoux, gastric washings for AFB, mcs & gene X-pert**

- **Vitamin** E, B6, B12 levels
- **CSF** – protein, cells
- **MRI** of brain (microcephalic)
- **Urine** metabolic screen, organic acids
- **CK**
- **DNA analysis** – if indicated

16. My approach to manage this pt would be:

- First appropriate history as above
- Manage the current chest infection
  - Antibiotics
  - Oxygen as per sats monitoring
  - Feeding – NGT if poor intake orally
- MDT approach – OT, physio, speech & social worker
- Hearing and vision assessment
- Exclude TB and do other investigations as above
- Further management as per diagnosis

Exam questions

1. You said there was no clonus - if it was present in this child – would it change your assessment?
   - No – he has already other cardinal signs of UMNL
2. What is unsustained clonus?
   - Clonus <1 yr (10-12) and > 1yr (6-8) is unsustained clonus
3. What are different types of nystagmus?
   - Horizontal
     - Cause may be toxins, vestibular, or cerebellar
   - Verticle
     - Cause may be brain stem lesion or child may have been on phenytoin
   - Rotatory
     - Cause may be visual impairement or increased sensitivity to light (albinism)
4. What are causes of ptosis?
   - Unilateral
     - 3rd nerve – neuritis
     - Horner's syndrome
     - Myasthenia
     - Congenital ptosis
   - Bilateral
     - Myasthenia
     - GBS (MFV)
     - Muscles (myopathies)
5. What is external and internal ophthalmoplegias?
   - External: related to eye momements
   - Internal: related to pupillary response

6. What are the causes of 3rd nerve palsy?
    - Trauma
    - Idiopathic
    - Central
        - Vascular lesions in brain stem
        - Tumours
        - Demylination
    - Peripheral causes
        - Compressive lesions
        - Tumors
        - Basal meningitis
7. What do you know about HIV encephalopathy?
    - Time line: 3 months at least – child should be HIV positive
    - Microcepahly – cerebral atrophy on neuroimaging
    - Pyramidal tract signs
    - Regression of milestones
        - Static – gains milestone late
        - Plateau – stuck at certain milestone
        - Progressive – loss of previously acquired milestones
8. Tell us about the anatomy of 7th cranial nerve?
    - Nucleus in pons (next to 6)
    - Leaves pons with 8 (cerebelopontine angle)
    - Enlarges to geniculate ganglion (facial canal)
    - From within facial canal gives off branches that supply strapidious muscle
    - Chorda tympani joins in facial canal
    - Leaves skul via stylomastoid foramin
    - Passes through middle of parotid gland and supplies to muscles of facial expression
9. What are LMN lesions of facial nerve?
    - Pontine lesion
        - Vascular
        - Tumors
        - Syringobulbia
        - Multiple sclerosis
    - Posterior fossa lesions
        - Acoustic neuroma
        - Meningioma
        - Chronic meningitis
    - Petrus temporal bone
        - Bells
        - Ramsay Hunt
        - Otitis media
    - Parotid gland
        - Tumor
        - Sarcoidosis

NEUROFIBROMATOSIS

CAFÉ AU LAIT SPOTS

- Normal variant in 19% of the population
- >5mm prepubertal
- >15mm postpubertal
- ≥5 lesions → pathological

NEUROFIBROMATOSIS

- AD 1/3000
- 50% are sponataneous mutations
- Type 1: chromosome 17
- Type II: chromosome 22

TYPE I:

Diagnostic criteria: ≥ 2 of the following

- 6 or more café au lait macules:
  - >5mm diameter in prepubertal and
  - >15mm diameter in postpubertal patients
- 2 or more neurofibromas (Schwann cell tumors)
- Presence of plexiform neurofibromas
- Freckling – axillary or inguinal regions
- Optic glioma
- 2 or more Lisch nodules (iris hamartomas)- usually develope later >5 years
- Distinctive osseus lesions example:
  - Sphenoid wing dysplasia
  - Thinning of long bones cortex (with or without pseudoarthrosis)
  - Bony rarefaction or overgrowth due to the presence of plexiform neuroma
- First degree relative with type I disease

TYPE II

Diagnostic criteria

- Bilateral acoustic neuroma (may be present with deafness), seen with imaging techniques OR
- A first degree with type 2 and either unilateral 8th nerve mass or 2 of the followings:
  - Neurofibroma
  - Meningioma
  - Glioma
  - Schwannoma
  - Juvenile posterior subcapsular lenticular opacity

No Lisch nodules in type II
Type II: AD - defect in long arm of chromosome 22
50% have café au lait spots but always less than 6
Intertriginous freckling rare
Does not present in childhood, mean age of onset – 20 years.
Lens opacities seen on slit lamp examination

CLINICAL FEATURES OF NEUROFIBROMATOSIS (short notes)

1. Café au lait spots

- Present in >90% of cases
- Smooth or irregular margin
- Significant if
  - 6 or more in number
  - of >5mm diameter in prepubertal or
  - of >15mm diameter in postpubertal patients
- Usually present at birth
- Increase size and number (1mm -15mm)
- Random distribution
- No threat to health

2. Freckling

- 1-3mm hyperpigmentation
- 2 types: Small café au lait spots present at birth throughout the body or develop later in intriginous area example axilla, groin
- EM shows macromelanosome
- Hyperpigmentation associated with plexiform neuroma which extends to midline often indicates that tumor involves spinal cord

3. Neurofibromas

- 3 types
  - Nodular and discrete (pedunculated skin neurofibromas)
  - Diffuse with extensive interdigitation with surrounding tissues
  - Plexiform (a network of nerves or veins) which are highly vascular congenital developmental lesions
- Histologically consist of neurons, Schwann cells, fibroblasts, vascular elements, mast cells and pigment cells
- Pregnancy and puberty leads to an increase in size and number

4. Lisch nodules

- Pigmented iris heamatomas (2 or more are significant)
- 94% of patients are > 6 years of age
- Increase in number with age, do not become symptomatic
- Not seen in normal persons and in those with type II

5. Macrocephaly

- May be absolute (OFC >97th percentile) or relative (head size disproportionately large for wt and height – data suggests post natal onset)

6. CNS tumours

- Include:

  - Optic gliomas & astrocytomas (slowly growing tumors consisting of astrocytes, star shaped cells of neuroglia and supporting structute of brain and spinal cord)
  - Acoustic neuromas (type II NF), neurilemmomas, menigiomas & neurofibromas
- Occurrence: 5-10%
- Most frequently detected in 1st decade
- Spinal tumours are frequently meningiomas

7. Pseudoarthrosis (PA)
- Incidence: in 0.5-1 % of patients – 50% of congenital PA are due to NF
- Discrepancy of length
- Big toe
- Tibia and radius are most often involved
- Severity ranges from asymptomatic to needing amputation

8. Kyphoscoliosis
- Incidence: in 2% of patients
- Involves lower cervical and upper thoracic spine
- Manifests by 5-15 years
- Often associated with paraveterbral neurofibromas

9. Height
- Mean: 25th percentile – 16% are <3rd percentile

10. Associated malignancies
- Neurofibrosarcoma, malignant schwannoma, Wilms tumour, rhabdomysarcoma, leukemia, neuroblastoma, medullary thyroid carcinomas, pancreatic adenoma
- Freq of pheochrmocytoma: <1% – virtually unknown in patients with neurofibromatosis
- Visceral tumours – in <1% of patients & may account for bleeding or obstruction

11. Ability
- 40% have learning disability, hyperactivity and school performance problems
- 2-5% have frank mental retardation
- 30-40% have nasal speech, reduced rate and hoarseness, breathlessness, monotone voice, tremor and varying loudness – cause unknown

12. Cerebrovascular disorders
- Cerebrovascular compromise occur due to neurofibromatous involvement of cerebral vessels, may get diffuse or focal cerebral symptoms

13. Hypertension
- May be due to involvement of renal artery by neurofibroma in <1% of patients or pheochromocytoma

14. Constipation

- 10% occurrence, due to disturbed autonomic innervations of colon

15. Pruritis

- 2 presentations – either skin overlying established cutaneous neurofibroma or preceding the development of local neurofibroma, aggravated by heat, improved by bath or shower and partial relief with antihistamines

16. Seizures

DEVELOPMENTAL DELAY

SYNDROMIC

Chromosomal deletions or additions, drugs, multifactorial

- Aicardi
- Huntingtons
- Carpenter
- Wilsons
- A betalipoproteinemia
- Hallervorden Spatz
- Mucopolysaccharidosis
- Tay Sachs
- PKU
- Fragile X
- Downs
- Trisomy 13/18
- Kleinfelter
- Drugs: alcohol, warfarin, isotretinoin
- Infections: rubella, CMV, toxo, HIV

NON SYNDROMIC

- Nutritional
- Neurocutaneous syndromes: SW, ataxia, telengiectasia, NF1
- Structural brain abn
    - Encephalocele
    - Porencephalic cyst
    - Schizencephaly
    - Lissencephaly
    - Hydrocephaly
- AD/AR microcephaly
- Complicated migraine
- Lennox Gastaut
- Mucopolysaccharidosis

DIFFRERENTIAL DIAGNOSIS OF CEREBRAL PALSY

According to the site of lesion or nature of lesion

- Acute
- Chronic -non progressive
- Chronic progressive

Acute

- Hypoxic ischemic: Post status epilepticus, post drowning, sever pneumonia
- Infectious: Meningitis, meningoencephalitis
- Trauma
- IEM: Urea cycle defects, carbamyle phosphate synthase deficiency (Ziai p 807)

Chronic non-progressive

- Antenatal: Stroke
- Perinatal: HIE
- Post natal: Infections, post infectious, drugs, toxin, post GE
- Congenital structures: Abnormalities of the brain

Chronic progressive

- Neurometabolic
    - Predominantly white matter (spasticity, ataxia, optic atrophy, peripheral neuropathy)
    - Predominantly grey matter (seizures, congnitive impairement, encephalopathy)
- Infections: RVD encephalopathy, TB, fungal,bacterial
- Malignancies
- Neurocutaneous syndromes
- Demyelinating disorders – predominantly white matter
- Chronic exposure to toxins – lead
- CNS Vasculitis – Moya Moya
- Global developmental delay without spasticity
- Nutritional
- Chronic deprivation
- Prolonged hospital stay

Question: what is CRASH syndrome?

C – Carpus callosum agenesis
R – Retarded growth
A – Adductor thumbs
S – Spasticity
H – Hydrocephalus
Also associated with Acardi Syndrome. Work-up: retinal examination (ophthalmic consultation), renal and cardiac US, X-ray spine, CXR (lung hypoplasia)

CHILD WITH HEMIPLEGIA

Aetiology and pathogenesis (B Nelson p849)

DEFINITION

- Postnatally acquired hemiplegia in a child who is neurologically unimpaired at birth excludes children with hemiplegia related to:
  - Prenatal factors e.g congenital malformations, chromosomal aberrations, prenatal infections
  - Perinatal factors e.g prematurity, birth trauma, perinatal infections
- In the neonatal and early infancy period, acquired hemiplegia is often confused with congenital disorders
- Congenital hemiplegia is often unrecognized until after 4-5 months age, the determining factor is the relative acuteness of onset

1. TRAUMA

- Occlusion of carotid artery, concussion or electrical injury
- Direct – falling on foreign object carried in mouth e.g. pencil/ lollipop. Latent period of 3-24 hrs during which carotid artery thrombosis develops
- Blunt injury to head and neck due to sudden extension of neck causing internal disruption and thrombosis of extracranial carotid artery. Latent period of 1-24 hrs between injury and onset of hemiplagia
- Fat embolism following vascular occlusion or DIC. Rare paediatric complication of long bone fractures

2. INFECTIONS

- Encephailitis of viral origin – sometimes complicated by herpes simplex (focal encephailitis with hemiplegia is frequent finding). Less commonly occurs with coxsackie, herpes zoster, polio, immunization with measles or rubella can result in focal encephalitis
- Post infectious (measles, rubella, mumps, varicella or influenza) and post vaccinal (rabies or pertussis) encephalitis causes perivascular demylination and may result in hemiplegia, seizures and coma
- Bacterial meningitis may be complicated by cortical vascular thrombosis with a predilection for one hemisphere
- Cervical lymphadenopathy secondary to ENT and paranasal sinus infection may involve adventitia of internal carotid artery with subsequent development of carotid arteries and intravascular thrombosis
- Rarely fungal infections e.g. aspergillosis and mucormycosis can cause cerebral infarction following internal carotid / middle cerebral artery occlusion. Consider in immunocompromised patients

3. CARDIAC DISAESE

- Cyanotic heart dx is often complicated by cerebral thrombosis – usually occurs in children <2 years old, a brain abscess rather than arterial thrombosis may be responsible for hemiplegia
- RHD / subacute bacterial endocarditis → emboli from cardiac vegetations → acute hemiplegia. Occasionally mycotic aneurysms may rupture to cause intracerebral or subarachnoid bleeding
- Arrhythmias especially atrial fibrillation favour the development of mural thrombi and therefore emboli and hemiplegia
- Hypertension: haemolytic uremic syndrome, nephrotic syndrome
- Myxomas (tumors composed of mucous tissue) of heart may present as unexplained sudden hemiplegia due to thromboembolic episodes from myxoma
- Prosthetic heart valves and MVP is associated with cerebral infarction

4. CONGENITAL VASCULAR ANOMALIES

- A-V malformations may rupture and form intracortical clot causing hemiplegia. Occasionally they may cause compression and destruction of brain parenchyma causing hemiplegia without rupturing →"steel phenomenon"
- Congenital looping, tortuisity or kinking of ICA may cause cerebral infarction by arterial occlusion associated with certain neck positions or by embolisation of thrombosis formed in areas of abnormal endothelium

5. SYSTEMIC DISEASES

- Hematological disorders:
    - Hypercoagulable conditions (factor V Liaden def, protein C& S def, antithrombine III def, and antiphospholipid antibodies)
    - Hypocoagulable conditions
    - Leukemia, haemophilias, ITP → increased riks of intracranial heamorrhage
    - Sickle cell dx has increased association with heamorrhage and occlusive cerebrovascular dx
    - Polycythemia and thrombocytosis may be complicated by cerebral arterial thrombosis
    - Haemorrhagic disease of the newborn
- Inflammatory arterial dx:
    - Most of the collagen vascular diseases especially SLE or PAN can cause hemiplegia secondary to arterial thrombosis.
    - Takayasus arteritis (commonest in females) can occasionally cause hemiplegia in childhood
- Metabolic disorders:
    - Hypoglyceamia can occasionally cause focal neurological signs.
    - Dehydration with/without hypernatreamia may have dural sinus and cerebral venous thrombosis with resultant hemiplegia.
    - In homocystinuria arterial and venous thrombosis occurs in large and small vessels resulting in focal neurological signs. Risk: 10-15%
    - Leigh's disease

6. OBSCURE AETIOLOGY

- Localized arteritis following URTI/unrecognised trauma to ICA in paratonsillar area may result in arterial occlusion. Difficult to ascertain precise cause.
- Moya Moya dx (can be caused by sickle cell dx or NF1) → bilateral occlusion of ICA at carotis siphon combined with bilateral arterial networks at base of brain. 70% cases occur in children <16 years. Children may present with TIA, hemiplegia, epilepsy and rarely SAH.
- Todd's paralysis following seizures

7. TUMORS

Brain stem gliomas, posterior fossa tumors, cerebral hemisphere neoplasm and tumors of basal ganglia

8. ACUTE HEMIPLEGIA OF CHILDHOOD

Also called as acute infantile hemiplegia – vascular occlusion due to unknown cause (B Nelson p 849)

AN APPROACH TO A CHILD WITH HEMIPLEGIA

HISTORY AND EXAMINATION

- Hx of onset and preceding events including trauma
- Family hx of neurological dx
- Birth hx
- Infections
- Drugs
- Milestones

- **General:**
  - Dysmorphism / chromosomal abnormalities
  - BCG
  - Neurocutaneous lesion
  - GCS/ Adelaide scale
  - Bony tenderness, gingival hypertrophy, xanthomas
  - Evidence of injury (to head, neck, pharynx)
- **Abdomen:**
  - Kidney (bruits, polycystic kidneys, Berry ancurysm), hepatomegaly, (CCF), splenomegaly (IE)
- **CVS:**
  - Pulses – if all palpable (emboli, CVA, Takayashus), BP, IE/CMO (mural thrombus), apex beat
- **ENT:**
  - Otitis, mastoiditis, abscesses
- **CNS:** Full CNS examination
- Acute onset with no seizures but with a change of state of consciousness
- Some cases of carotid A thrombosis or migraine may have intermittent pattern. There may be transient episodes of weakness with decreased palpability of contralateral ICA.
- Congenital hemiplegia may become apparent only after the age of 4-5 months

ABRUPT ONSET

- Most common mode with seizures, high fever, coma and hemiplegia. Often associated with hemianopia and aphasia. Severity and duration of seizures relates to the degree of ultimate motor impairment. If multiple seizures and age of onset is <2 years then 50% may develop epilepsy
- Almost all with prolonged focal/gerneralised seizures have permenant motor deficit, recurrent seizures, MR and hyperkinetic behaviour
- MR occurs in 30-50% of these survivors
- <20% whose hemiplegia began without seizures develop epilepsy, MR and behaviour and learning problems

- Prognosis: depends on age of onset, severity of hemiplegia and neurologic findings. Hemiparesis may disappear rapidly or regress over 3-4 months or persist indefinitely. Weakness for 2-3 weeks after onset is indicative of residual deficit. Dysphasia more common in child >4 years with a dominant hemispheric lesion
- Age <2 yrs, have poor prognosis
- F:M = 3:2

ACUTE ONSET

1. Arterial/venous occlusion

- **Embolism** – from myxomas, arrhythmias, cyanotic heart dx in child < 2 years. IE/mycotic aneurysm, prosthetic valves, MVP, vascular occlusion/DIC may → fat embolism
- **Thrombosis:** Hypoglycaemia, dehydration, hypernatraemia – sinus and cerebral venous thrombosis. Homocystinuria – small and large vessel arterial and venous thrombosis. Risk: 15%
- **Migraine** – basilar artery
- **Trauma:** Falling on FB → carotid A thrombosis in 3-24 hours. Blunt injury to neck/torsion with injury to ext CA
- **Congenital vascular malformation:** AV malformation with bleeding or compression without bleed (steel phenomenon). Looping/tortuosity of ICA may result in arterial occlusion in certain neck positions or thrombus formation in areas of abnormal epithelium

2. Vasculitis

- **Moya moya**
- **Infection:** Adenopathy/ENT pathology with involvement of adventitia of carotid A, viral encephalitis, bact meningitis with cortical vascular thromobosis, fungal infection – carotid / MCA occlusion with infraction
- **Post infectious:** measles, mumps, rubella, vaccinia

3. Hypertension with bleed

4. Systemic dx/neoplasms

- Heamatological: Leukemia, heamophilia, thrombocytosis, sickle cell
- Collagen vascular dx – SLE, PAN, Takayasus (esp females)

SLOW ONSET

- Space occupying lesions
- Tuberculoma
- Cysts
- Malignancy

INVESTIGATIONS – guided by clinical examination

- Start with MRI/MRA, EEG, or CT with angio (Dr Mubaiwa) → if normal or no signs of increased intracranial pressure do LP and send CSF for:
    - mcs & chemistry
    - neurotropic viruses (herpes simplex, varicella zoster, enteroviruses, CMV and Epstein-Bar virus)
    - AFB
    - CFT (complement fixation test) for neurocysticercosis
- Blood for U/E, blood gas, blood suger, ammonia, lactate, LDH, LFTs and cardiac enzymes (if indicated)
- Stroke work-up
    - FBC, diff smear, platelets – if anaemia do sickle cell prep
    - Factor V Leiden
    - Antithrombine III
    - Lipid profile
    - PT, APTT, INR
- TPHA / tissue biopsy (dark field microscopy → spiroketes)
- HIV PCR/ ELISA
- Blood culture
- Collagen screen – antiphospholipid antibodies
    - Lupus anticoagulant antibodies
    - Anticardiolipid antibodies
- Serum protein electrophoresis
- MSU for mcs, dipstix (haematuria), urine aminoacids (homocystinuria), organic acids
- ESR, Mantoux, CXR
- ECG to evaluate cardiac arryrhemias
- Cardiac echo / TEE (transesophageal echocardiograme)
- Holter monitor (recording heart rhythm over 24 hr period)
- Aortic and cerebral angiography – occlusive vascular dx, arteritis

MIDDLE CEREBRAL ARTERY STROKE

Common causes:

- Haemorrhagic (intracranial, subarachnoid)
- Carotid or vertebral dissection
- Cardiovascular disease
- Co-agulopathies

Clinical presentation

Main trunk

- Contralateral hemiplegia
- Eye deviation towards side of MCA infarct due to damage to lateral gaze center
- Contralateral hemianopia
- Contralateral hemianaesthesia

Trunk incl dominent hemisphere

- Global aphasia
- Impared perception of deficits

Superior division infarct

- Contralateral deficit with involvement of upper extremity & face
- Partial sparing of contralateral leg and foot

Inferior devision infarct

- Wernick aphasia
- Superior quadrantanopsia (loss of vision of $1/4^{th}$ of visual field)
- Homonymous hemianopia
- Relevant temporal lobe infarct can lead to agitated and confused state

Specific neuroligic squalae

- LOC or seizures – sec to oedema, due to subsequent brain stem herniation
- Partial hemiparesis
- Movement disorders (athetosis, chorea and dystonia)
- Hemianopia
- Contralateral oedema of hand and foot arising within hrs of infarct lasting up to weeks → autonomic dysfunction due to MCA srtoke

Left hemisphere infarct

- Broca-aphasia (exspressive or motor)
- Wernick aphasia (receptoive or sensory)
- On verbal commond pt is uncoordinated and unable to perform simple tasks

Right hemisphere infarct

- Behavioural abnormalities 9neglect and impersistanmce)
- Extinction – in attention to one stimulus when 2 stimuli are pre3sented simultaneously
- Topographic memory deficit
- Confusion and delirium

Differential diagnosis:

- Conversion disorder
- Hypoglycaemia
- Migraine headach
- Subdural hematoma
- Focal seizures / tumors

Investigations:

1. Ultrasonography:
   - Transcranial Doppler ultrasonography – MCA patency
   - Carotid duplex
   - Doppler ultrasound for DVT

2. CT:
   - Performed being accessible, fast and sensitive for confirming haemorrhage
   - Less sensitive than MRI for diagnosis of stroke within few hours
   - CT angio for perfusion status of brain parenchyma

3. MRI:
   - Limited access, high cost
   - Provides 2 different types of images
   - Diff weighted – can detect stroke in 15-30 minutes of onset
   - Perfusion weighted show active zone of ischaemic injury

NEONATE WITH BIG HEAD

Causes of macrocephaly

1. Abnormally thickened skull / soft tissue oedema
    - Rickets – vitamin D deficiency
    - Osteogenesis imperfacta
    - Osteopetrosis
    - Achondroplasia
    - Fibrous dysplasia
    - Cleidocranial dysostosis
    - Cephalhaematoma
    - Caput succidanium
2. Oedema of brain tissue, meningitis and subdural collections
    - Toxic – lead, vitamin A, tetracyclins
    - Metabolic – galactosaemia, glutaric aciduria type 1
    - Pseudotumor cerebri
    - Leukodystrophy
        - Canavan's spongy degeneration
        - Alexander's disease
    - Subdural accumulation
        - Head injury
        - Haematoma (NAI)
        - Effusion
    - Infections
        - Perinatal – TORCH, syphilis, HIV
        - Post natal – meningitis, encephalitis
    - Vascular
        - IVH
        - Stroke
3. Megalencephaly
    - Primary
        - Familial
        - Gigantism
            - Fragyle X
            - Cerebral – Soto's
            - Pituitary
        - Neurocutaneous syndromes – tuberous sclerosis
        - Cutaneous haemangioma Syndromes
            - Disseminated hemangiomatosis

        - Klipple – Trenaunany – Weber Syndrome
        - Sturge Weber Syndrome
- Secondary
    - Tay- Sachs disease
    - Generalised gangliosidosis
    - Mucopolysaccaridosis
    - Metachromatic leukodystrophy
- Hydrocephalus
    - Obstructive
        - Congenital malformations:
            - Arnold-Chiari
            - Dandy-Walker
            - Congenital hydrocephalous (acqueduct stenosis)
            - Spina bifida
        - Neoplasms (tumours, intracranial cysts)
        - Aneurysms
    - Non-obstructive
        - Fibrosis – secondary to inflammation or haemorrhage
        - Malformations
        - Neurocutaneous syndromes (NF1, tuberous sclerosis)
        - Papilloma of choroid plexus
- Constitutional macrocephaly (no evidence of increased intracranial pressure)

Average figures of OFC

35cm @ birth
47cm @ 12 cm (another 12 cm)
49cm @ 2yrs (another 2 cm)
50cm @ 3 yrs
52cm @ 6 yrs
53cm @ 10 yrs
56cm @ adulthood

Macevan sign

Percussion of skull may produce a crackpot or macewen sign – indicating separation of sutures

- Acqueductal stenosis
- Abnormal narrowing of acqueduct of Sylvious / forking
- Sex linked recessive in small percentage of cases
- Associations: spina bifida occulta, neurofibromatosis, acqueductal gliosis
- Pathogenesis: may be intrauterine congenital infections, neonatal meningitis, subarachnoid haemorrhage

Dandy Walker Malformation

Cystic expansion of 4th ventricle in posterior fossa which results due to developmental failure of the roof of the 4th ventricle during embryogenesis

- 90% have hydrocephalus
- Others: agenesis of posterior cerebellar vermis & carpus callosum
- Most children have long tract signs, cerebellar ataxia and delayed motor & congenital milestones
- If HCP present – DWM is managed by shunting the cystic cavity & ventricles

Chiari formation

Type 1

- Symptoms in adolescents & adulthood
- Usually not associated with HCP
- Pathogenesis: obstruction of caudal portion of 4th ventricle during fetal development
- Signs and symptoms
    - Recurrent headach and neck pains
    - Urinary frequency
    - Progressive lower limb extremity spasticity
    - Displacement of cerebellar tonsils into cervical canal

Type II

- Progressive hydrocephalus
- Myelomeningocele: Symptoms during early in infancy: strider, weak cry, apnoea
- Indolent form consists of abnormal gait, spasticity and increase incordination
- Skull X ray → small posterior fossa, widened cervical canal
- CT brain and MRI with contrast → cerebellar tonsils protruding downward into cervival canal and hind brain abnormalities

Canavans leukodystrophy

AR: Progressive damage to nerve cells and brain

Dany's Drash

Abnormal genetalia, Wilms tumor

Meckle-Gruber Syndrome

- AR
- Characterised by:
    - Ooccipital encephalocele
    - Cleft lip or palate
    - Microcephaly
    - Abnormal genetalia
    - Congenital nephrosis
    - Polydactyly
- Encephalocele may be diagnoses in-utero by ultrasound measurement of BPD and alpha fetoprotein levels

CHILD WITH SMALL HEAD

Causes of microcephally

1. Genetic abnormalities

- Chromosomal/ other genetic abnormalities
  - Trisomies – 21, 13, 18
  - 5p- Cri-du-chat
  - Angelman's Syndrome
  - Prader-Willi Syndrome
  - Smith – Lameli – Opitz Syndrome
  - Beckwith Weidemann Syndrome
- Primary microcephaly
  - Autosomal recessive (microcephaly vera)
  - AD microcephaly
  - Sex linked microcephaly
- Malformations
  - Holoprosecephaly
  - Hydrancephaly
- Neuromigrational disorders
  - Lissencephaly
  - Schizencephaly
  - Agenesis of carpus callosum
- Metabolic disorders
  - Phenylketonuria
  - Hypophosatasia
- Developmental disorders
  - Craniosynostosis totalis
  - Cerebral dysgenesis
  - Cerebral hypoplasia
- Neurometabolic Syndromes
  - Lysosomal disorders
  - Peroxisomal disorders
  - Mitochondrial disorders
  - Grey matter dx
  - White matter dx
  - Basal ganglia dx
- Neurodegenerative brain diseases
  - Krabbes
  - Ceroid lipofuscinosis

    - Infantile neuroaxonal dystrophy
    - Palizaeus- Marzbacher disease
- Post natal onset
    - Aicardi's
    - Angelmans
    - Fanconi's
    - Rubinstein Taybi
    - Rett syndrome

2. Secondary or acquired

- Prenatal insult – maternal / perinatal factors
    - Intrauterine – TORCH, syphilis, HIV, varicella
    - Teratogens – drugs, radiation, alcohol (foetal alcohol syndrome)
    - Sever maternal illness / maternal phenylketoneuria / sever maternal malnutrition
- Post natal onset
    - Perinatally acquired – primary acquired herpes simplex infection, encephalitis, bacterial meningitis
    - Head injury, perinatal hypoxia, stroke, periventricular leukomalacia
    - Undernutrition – chronic illness (renal, cardiac, pulmonary disease)
- Endocrine abnormalities
    - Hypothyroidism
    - Hypopituitarism
    - PKU
    - Mum untreated for PKU

Neurometabolic disorders

Disorders with accumulation of small metabolic componds (amino acids, organic acids, ammonium, purines and saccarides – also called clinical imaging syndromes.

Clinical signs

- Muscle tone – increased or decreased
- Ataxia
- Dystonia
- Tendon reflexes may reflect involvement PNS
- Neuro-ophthalmological assessment
- Vision (retinitis pigmentosa)
- Eye movements
- Sensory impairement
- Hearing

Investigations

- Neuroimaging
- Biochemical studies
- Haematology / immunological study
- CSF examination
- Tissue examination
- Skin, rectral, nerve, brain, muscle biopsy
- Bone Xray
- Genetic studies

Aicardi syndrome

Triad of:

- Infantile spasm-in-flexion
- Total or partial agenesis of carpus callosum
- Variable ocular abnormalities

Other features may be:

- Abnormal facies
- Cleft lip & palate
- Vertebral body abnormalities
- Neuronal migration
- Moderate to sever mental retardation

Angelman syndrome (B Nelson p226)

Chromosome 15q.11

- Characteristic facial appearance
- Moderate to sever mental retardation
- Absence of speech
- Ataxic movement of arms and legs
- Characteristic craniofacial appearance
- Seizures disordercheracterised by laughter
- Sleep disturbance

Rubenstein Taybi Syndrome (Nelson p192)

Disordrer marked clinically by

- Broad thumbs
- Great toes
- Characteristic facies
- Sever mental retardation
- Speech difficulties
- Genetic error on Chromosome 15
- Facial features (pub med health)
- Small upper jaw with narrow palate
- Prominent beaked nose

- Wide set down slanting eyes
- Low set malformed ears
- Strabismus, cataractys, tear duct obstruction, macro/microcephaly
- Other features
- Low muscle tone
- Growth deficiency
- Undescended testes
- Hirsutism

Common problems

- Sever constipation
- Ear & URTI
- Dental problems

Rett syndrome

Neurodevelopmental disorder ch by:

- Loss of acquired fine & gross motor skills
- Loss of acquired ability to engage in social interaction
- Development of stereotypic hand movements
- Scoliosis

Fanconi's syndrome

Common causes: cystinisis and drugs like Epilim, Ifosfamide

- Generalized dysfunction of proximal tubules along with renal wasting of bicarbonate which causes:
    - Glycosuria
    - Aminoaciduria
    - Excess urinary loss of phosphate and uric acid

DRESS syndrome (Nelson p268)

- Anticonvulsant hypersensivity syndrome: **D**rug **R**ash, **E**osinophilia, **S**ystemic **S**ymptoms
- It is multisystem reaction that appears from 1-4 months after starting phenytoin, carbamazepine, phenobarbitone or primidone
- Although initially described with anticonvulsant therapy other drugs also have been implicated i.e. antibiotics
- Mucocutaneous eruption may be identical to erythema multiform, SJS, or toxic epidermal necrolysis but reaction also typically includes:
    - Lymphadenopathy
    - Fever
    - Hepatic, renal & pulmonary dx
    - Eosinophilia
    - Leukocytosis
- Treatment – as per errythema multiform

- Identify drug – discontinue ASAP
- Strict reverse isolation
- Meticulous fluids and electrolytres therapy
- Use of air fluid bed and daily culture
- If secondary infection evident – treat with syst antibiotics
- Skin care – normal saline
- Hydrogel dressings – reduce fluid loss and pain
- Glucocorticoids
- Immunoglobulines IVI – have been used with success but this remains controversial

PARAPLEGIA

APPROACH

- **History:** Trauma, gradual/sudden onset, progressive, pain and preceding viral infection
- **General examination:** Nutrition, BCG, Mantoux, LN, colour, bossing, overgrowth of bone, trophic ulcer and bed sores
- **CNS**
  - Increased intracranial pressure
  - Meningism
  - Neurocutaneous stigmata
  - Motor status (paraplegia, paraparesis, power, tone)
  - 2-point discrimination (vibration, Rombergs)
  - Do PR – check incontinence
  - Spine – gibbus, tenderness, hair, lipoma, kyphosis, scoliosis, heamangioma, LL deformities, listen to spine (bruits in AV malformation)
- **Abdomen:** Masses, hepatomegaly, splenomegaly, lymphoma, secondaries from neuroblastoma
- **Chest:** Deformities, movement
- **CVS:** Sign of SBE
- **Site of lesion:** UMNL vs LMNL
- **Nature of lesion:** With or without sensory level

NATURE OF LESION

- **UMNL signs:** Hypertonia, brisk reflexes, spasticity, Babinski positive, clonus, no fasciculations, no marked wasting

- **LMNL signs:** Hypotonia, areflexia, flaccidity, normal planters, fasciculations, wasting

- **No sensory level → UMNL**
  - Superior saggital sinus thrombosis
  - Hereditary spastic paresis associated with Human T Cell Lymphocytic Virus1(HTLV1)
  - Parafalx lesion: X-linked, optic atrophy, bladder incontinence
  - Subacute combined degeneneration of cord, vit B_{12} deficiency, absent ankle jerks, posterior column involvement
  - CP: Little dx, diplegia
  - Devic dx also called neuromyelitis optica: consists of optic neuritie & transverse myelitis
  - GBS: areflexia, symmetrical flaccid ascending paralysis
  - Polio: asymmetrical muscle weakness

- **With sensory level → LMNL**

1. **Myelopathy:** Cord problems
    - **Congenital**:
        - Dystrophic states
        - Syringomyelia
        - Hydromyelia
        - AV malformations
    - **Acquired**
        - Infections:
            - Neurotrophic viruses (entero, herpes, varicella, CMV, EBV)
            - Bacterial infections
                - Acute with suppuration (Staph)
                - Chronic (TB myelitis)
                - Fungal (Cryptococcus)
                - Parasitic (Schistosomiasis, Cysticercosis)
        - Neoplasms: Glioma, ependymoma
        - Vascular: Heamangioma, heamangioblastoma
        - Trauma: Heamatomyelia
2. **Veterbral**
    - **Congenital**: Kyphosciolosis
    - **Acquired**
        - Traumatic
        - Infective (Staph, Ecoli, TB)
        - Malignancy: Primary/secondary, leukemia, lymphoma, histiocytosis, neuroblastoma, Wilms tumor
3. **Extradural** (see diagram Nelson 18th ed p2528)
    - **Trauma:** heamorrhage
    - **Infections:**
        - Acute pyogenic →abscess. Chronic →TB cold abscess, hydatid cyst
    - **Neoplastic:** leukemia, lymphoma
    - **Cysts:** meningeal, hydatid
4. **Intradural**
    - **Intramedullary** – see myleopathy and transverse myelitis
    - **Extramedullary**
        - Infection: TB arachnoiditis
        - Arachnoid cysts
        - Meningiomas
        - Neurofibromatosis
        - Meningeal infiltration: leukemia
    - **Miscellaneous**: multiple sclerosis
5. **Anterior spinal artery compression:** posterior column spared, sensory level

INVESTIGATIONS

- Radiological spine: Myelogram, MRI
- Mantoux, CXR
- Heamatological: FBC, CRP, blood culture, ESR
- Miscellaneous: CSF for AFB, mcs, cryprococcal, cysticercosis
- Multiple sclerosis: oligoclonal bands

CHRONIC CARE OF PARAPLEGIC CHILD

- Following acute spinal cord disease get paraplegia – initially flaccid then spastic with appearance of spasms and decubitus ulcers.
- Frequent turning - use air mattresses
- Bladder catherisation, may get chronic UTI with renal and bladder calculi

ANTERIOR SPINAL CORD LESIONS

1. **Spinal cord trauma:**
    - Breech deliveries
    - Accidents
    - Diving injuries
    - Fractures
    - Dislocation of vertebrae
2. **Atlanto-occipital dislocation:**
    - Trauma in congenital spinal malformations
    - Metabolic diseases/chondroplasiasis
    - Trisomy 21
        - Progressive weakness and gait disturbances
        - Spastic paresis of arms and legs
        - Treatment → reduction of dislocation
3. **Epidural abscess:**
    - Staph
    - TB osteomylitis of spine with extension
    - Pain & percussion tenderness over abscess
    - May get paraparesis and loss of bladder & bowel control with sensory level
    - Diagnosis → CT myelogram with LP, MRI
    - It is neurosurgical emergency
4. **Vascular abnormality of spinal cord:**
    - AV malformations
    - Venous angiomas
    - Telangiectasia
    - Get acute spinal cord dysfunction with bloody CSF and increased protein
    - Diagnosis by myelography
5. **Transverse myelopathy:**
    - Segmental cord dysfunction
    - Rapid onset within hours without evidence of compressive lesion or haemorrhage
    - May be caused by vascular occlusion with necrosis of cord, demyelinating dx or viral illness
    - Characterized by back pain, paraparesis, sensory level, inability to void
    - CSF – normal or mild elevation of protein and cells
    - If posterior columns intact then there is anterior spinal artery occlusion
    - Has sensory level
    - Natural history → recovery but may take 2 years
6. **Hereditary spastic Paraparesis:** Associated with HTLV1
7. **Subacute cord degeneration**
8. **Vit B12 def:**

- Absent ankle jerks. Poterior columns involvement leads to ataxia, paraesthesia, hyporeflexia, Babinski response, clonus, coma, peripheral neuropathy and dementia

9. **Devics Disease:** consists of optic neuritie & transverse myelitis
10. **TB spine:** Potts dx, TB spondylitis
    - Originates in the body of vertebrae and cause distruction of all tissues of articulation
    - Usually spinous processes and posterior arches unaffected
    - Kyphosis is most common mid-thoracic lesion
    - Scoliosis of lower thoracic followed by lumbar and cervical
    - Paraplegia is common – upper thoracic/cervical involvement
    - Psoas abscess
    - Cold abscess may open into pharynx/retropharyngeal abscess or above the clavicle

Clinical manifestations

- Persistent/intermittent pain
- Pain increases on pressure over the head
- Avoids bending movements – lies on abdomen
- Cervical lesions – holds head stiffly
- Non TB osteomyelitis – increased toxicity

Management

- Majority improves with minimal disability
- Paraplegia may resolve completely
- Reparartive processes may not begin for 1-3 years
- May need to apply Bradford frame cast until no active lesion
- Total duration 18 months with anti-TB treatment

SHORT NOTES

Syringomyelia (Stephenson p162)

It is triad of:

- Pain and temperature loss
- UMN signs in lower motor
- Atrophy and areflexia of arm

There may be scoliosis due to weakness of paravertebral muscles)

Saggital sinus thrombosis

- Complication of severe diarrhea/dehydration
- Obstruction leads to cerebral swelling, increased intracranial pressure with stupor, coma, bulging anterior fontanelle
- Thrombosis may extend to cortical veins leading to heamorrhagic infarcts of brain

May get seizures and quadriparesis, encephalitis or metabolic encephalopathy following water intoxication

Multiple Sclerosis (Nelson p2505)

Definition: A chronic and gradually remitting-relapsing disorder characterized by multiple white lesions in CNS separated by time and location in the brain

- Only 5% of all cases of MS occure before the age of 18 yrs
- Cause: unknown. But interactive, genetic and immunologic and infectious factors may be responsible
- Presenting signs:
    - Unilateral weakness with UMN signs
    - Sensory abnormalities
    - Ataxia
    - Paraesthesia of lower limbs and distal portions of the hands, feet and face
    - Headach, fatigue and dysarthria
    - Mylopathy with sensory level & neurologic bladder
    - Visual symptoms
        - Diplopia
        - Nystagmus
        - Sudden visual loss due to optic neuritis

Diagnosis:

- CSF: often contains oligoclonal bands
- MRI: neuroimaging of choice
    - Small plaques of 3-4 mm in brain stem and spinal cord
    - T2 enhancing lesions in corpus callosum & periventricular white matter

Treatment:

- High dose IV methylprednisolone
- Disease modifying interferion therapy (interferon beta)

Rehabilitation – especially for neurogenic bladder

Transverse myelitis (Nelson p2529)

Abrupt onset of progressive weakness & sensory disturbances in lower limbs

- Hx of preceding viral infection accompanied by fever and malaise
- Cause: EBV, herpes, influenza, rubella & varicella, Lime dx and mycoplasma pn
- Pathogenesis: 3 hypothesis
  - Cell mediated auto-immune response
  - Direct invasion of virus to spinal cord
  - Autoimmune Vasculitis

Clinical manifestations

- Low back pain and abdominal pain
- Paresthesia and weakness of leg muscles and flaccidity
- Sensory level – usually mid thoracic region
- Pain & light touch sentaions → affected
- Joint & vibration sense → preserved
- Sphincter disturbances are common → need catheterisaion
- Fever and nuchal rigidity
- Neurologic deficit evolve for 2-3 days then plateaus with flaccidity – gradually changing to spasticity with development of UMN signs in lower limbs

Differential diagnosis

- Meningitis
- GBS
- Polio
- Davics dx
- Spinal cord neoplasm
- Epidural abscess
- Demyelinating disorder
- Vascular malformation

Diagnosis

- CSF: Moderate lymphocyte pleocytosis, normal or slightly elevated protein levels
- MRI:
  - T_2 hyperintense
  - T_1-iso or mildly hypointense fusiform swelling extending over @ least 3-4 vertebral levels usually located in the thoracolumbar region

Treatment

- Bladder care
- Physiotherapy
- High dose methyleprednisolone
- Spontaneous recovery weeks to months in 40-50% of cases

APPROACH TO LOWER MOTOR NEURON DISORDERS

1. Spinal cord
2. Anterior horn cell
3. Peripheral nerves
4. Neuromuscular junction
5. Muscle
6. Metabolic

1. Spinal cord

- **Acute spinal cord injury**:
  - Get sensory & motor level
  - Disturbed bladder & bowel function
  - Local spinal pain & tenderness
- **Transverse myelitis:**
  - Follows mild febrile illness
  - Present with spinal shock initially followed by back pain
  - paraparesis, sensory level, inability to walk
  - CSF: moderate lymphocyte pleocytosis, normal or slightly elevated protein levels
  - Diagnosis by CT myelogram or MRI
  - Has LMNL signs at the site of lesion and UMNL signs above the site
  - When posterior column functions are spared occlusion of anterior spinal artery is most likely
  - Corticosteroid therapy – equivocal
  - Natural hx: recovery may take upto 2 years

2. Anterior horn cell

- **SMA**
- **Polio**
  - 95% have asymptomatic infection
  - May prsesnt with non specific febrile illness or
  - With complications like:
    - malena
    - acute gastric dilation
    - mild hypertension
    - convulsions
    - cardiac irregularities
    - pulmonary oedema/embolism
    - hypercalciuria with calculi
    - myocarditis
    - encephalitis

3. Peripheral nerves: get pins and needles, signs of LMN and may get thickened nerves

- **Guillian barre syndrome:**
  - Ascending – feet to face

    - Symmetrical flaccid motor paralysis with areflexia
    - Follows resp tract / GI infection e.g EBV, mycoplasma, enteroviruses
    - Bulbar, resp and facial muscles may be involved
    - Sensory involvement unusual
    - Absence of pain, sensory level and normal bowel and bladder function distinguish it from Transverse myelitis
    - 40% get disturbance of BP, perspiration, tachycardia and arrthymia – autonomic involvement which may be fatal
    - **CSF:** albumino-cytological dissociation. Protein increased day 10-14 with cells <50
    - **Treatment**: symptomatic, intensive care monitoring, plasma exchanges, steroids of no benefit. Polygam for chronic relapsing type. Poor prognostic signs → rapid onset, need for ventilation, plateau 16-18 days
- **Drugs and toxins**: diphtheria
- **Leprosy**: patchy areas of anaesthesis and sensory loss

4. **Neuromuscular junction:**
    - Myasthenia gravia: fatiguability, may have depressed reflexes
    - Botulism
    - Insecticide (organophosphate poisoning)
    - Tick bite paralysis
    - Snake bite
5. **Muscle –** Myositis:
    - May present with pain & swelling of muscles
    - Cause may be viral (CMV, EBV, entero, coxacchi, echo, H1N1), bacterial (staph), treponemal or connective tissue dx (SLE, dermatomyositis)
6. **Metabolic**
    - **Adrenoleukodystrophy (ALD):** white matter dx
    - **Acute porphyrias** (Nelson p640)
        - **Acute intermittent:** presenting symptoms are neurologic, exacerbated by drugs (p450 inducers), progesterone and dietary restrictions. Screening test: urinary porphobilinogen
        - **Porphyria cutania tarda:** skin blistering and fragility. Screening: plasma or urine porphyrins
        - **Erythropoetic:** get aneamia, non-immune hydropes & hyperbilirubineamia in early infancy and non blistering photosensitivity after sun exposure in early childhood. Screeining: erythrocytes or plasma porphyrins
    - **Diabetes:** Long standing – uncontrolled. Microangiopathic and metabolic disturbances are considered to be responsible for development of various forms of diabetic polyneuropathy (Berek et al. 1994)
    - **Uraemia:** Signs and symptoms of kidney dx. Fatigue, peripheral neuropathy, seizures, restless legs, decreased mental acuity and sleep disturbances.

Causes of AFP (Modified from Queenland Health Guidelines 2011)

Peripheral neuropathy

- Guillain-Barré syndrome
- Acute axonal neuropathy
- Neuropathies of infectious diseases (diphtheria, Lyme disease)
- Acute toxic neuropathies (heavy metals, snake toxin)

Anterior horn cell disease

- Acute anterior poliomyelitis
- Vaccine-associated paralytic polio
- Other neurotropic viruses (eg. enteroviruses and herpesviruses)

Muscle disorders

- Polymyositis, dermatomyositis
- Periodic paralyses
- Corticosteriods and blocking agents
- Mitochondrial diseases (infantile type)
- Post viral myositis

Systemic disease

- Acute porphyrias
- Critical illness neuropathy
- Acute myopathy in ICU patients

Acute Myelopathy

Cord compression

- Tumour / trauma
- Paraspinal abscess
- Haematoma
- Vascular malformation with thrombosis/bleeding

Demyelinating diseases

- Mmultiple sclerosis
- Transverse myelitis
- Acute disseminated encephalomyelitis (ADEM)

Ischaemic cord damage

- Anterior spinal artery syndrome
- Peri-operative complication

Disorders of neuromuscular transmission

- Myasthenia gravis
- Botulism
- Organophosphate poisoning
- Tick bite paralysis
- Snake bite

APPROACH TO PERIPHERAL NEOPATHIES OF CHILDHOOD

- Interruption of axon distal to cell body leads to axonal Wallerian degeneration
- Involvement of Scwann cell leads to demyelination e.g diphtheria and lead poisoning
- Distal muscles of arms and legs are commonly affected
- Get pins and needles
- Look for thickened nerves

CLASSIFICATION ACCORDING TO AETIOLOGY

HEREDITARY

1. **Hereditary sensory neuropathy**
    1. **HSN I** – radicular neuropathy
    2. **HSN II** – familial dysautonomia (Riley Day)
    3. **HSN III** – associated with anhydrosis

2. **Hereditary sensory motor neuropathy**
    - Charcot Marie Tooth Type I:
        - AD
        - Occurs after 6 years age
        - Peroneal nerve affectation with muscle atrophy
        - Chronic neuropathy with distal limb weakness, wasting, atrophy and foot deformities
        - Clinical features:
            - Pes cavus (differential diagnosus → Frederichs ataxia, spina bifida, cauda equine lesions, diastematomyelia, Hurlers)
            - Deformities of feet, ankle weakness with weak dorsifklexion → foot drop and frequent falling, high arched feet
            - Complaints of paraethesias with mild to moderate sensory loss in hands and feet
            - Slow progression with involvement of hands and forearms
        - Diagnosis – severely decreased NCV & hypertrophic changes on nerve biopsy
        - No specific treatment
        - Braces to maintain feet in dorsiflexion
        - Early surgery contraindicated

    - Charcot Marie Tooth Type II:
      Extensive degeneration of AHC leading to axonal degeneration

    - Type III – Dejerine Sotta:
        - AD disorder of cerebroside metabolism
        - Early onset with markedly enlarged nerves and segmental demyelination

- Present with delayed walking and progressive weakness of extremities
- CNS involvement occurs with nystagmus, hearing difficulty and abnormal pupil reflexes
- Urinary incontinence and pes cavus
- Spinal cord involvement – get affected by vibration and position.

Type IV – Refsums disease:
Abnormal phytannic acid metabolism
Clinical features:

- Retinitis pigmentosa
- Deafness
- Cerebellar ataxia
- Peripheral neuropathy
- Icthyosis
- Muscle weakness
- Cataracts
- Increased CSF protein

ACQUIRED

1. **Guillian Barre syndrome:** Classical ascending neuropathy with areflexia, minimal sensory loss and probable associons with autonomic dysfunction
    - **Miller Fischer variant**: A cranial nerve variant of GBS. Comprises of opthalmoplegia, nystagmus, ataxia, areflexia
    - **Chronic relapsing variant**
2. **Metabolic:** Diabetes (late onset), amyloidosis, uraemia, vit B complex def (B1, B6 & B12), vit E def (ataxia, areflexia, opthalmoplegia and sensory neuropathy), porphyria and hypoglycaemia
3. **Degenerative**
    - **Krabbe dx:** present in infancy with increased CSF protein and rigidity/flaccidity
    - **Metachromatic leukodystrophy:** aryl-sulfatase def, occurs in children <2yrs with distal muscle weakness, absent ankle jerks, abnormal gait and UMNL
4. **Drugs and toxins**
    - Drugs: INH, tetracycline, kanamycin, hydrallazine and vincristine
    - Toxins: Heavy metals like Hg & Pb
    - Lead poisoning with Fe def anaemia (basophilic stippling)
        - Neurodevelopmental and cognitive defect
        - Colic and nephropathy Poor school performance
        - Encephalopathy and distal motor peripheral neuropathy
        - Diagnosis by blood levels and basophilic stippling in FBC smear
        - Treatment: Removal of source, penicillamine and chelation
        - Specific treatment: Ca EDTA / BAL; D-penicllinamine
5. **Neoplasms:** Hodgkins dx, neurofibromatosis (types 1&2), and leukemia
6. **Vasculitis:** Mixed connective tx dx, SLE, rheumatoid arthritis, dermatomyositis
7. **Amyloidosis:**

- Comprises a group of diseases ch. by extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues (Nelson p1033)
- Get deposition in kidneys resulting in massive proteinuria, heamaturia, nephrotic syndrome and renal failure with peripheral neuropathy
- Get deposition in liver and spleen resulting in hepatospleenomegaly, chronic diarrhea, GIT bleeding, abdominal pain, anaemia and malabsorption
- Diagnosis is clinical
- Biopsy of rectal and gingitivitis areas when stained with Congo red shows specific amyloid protein
- Die from renal failure

8. **Acute porphyrias** (Nelson p640)
   - **Acute intermittent:** presenting symptoms are neurologic, exacerbated by drugs (p450 inducers), progesterone and dietary restrictions. Screening test: urinary porphobilinogen
   - **Porphyria cutania tarda:** skin blistering and fragility. Screening: plasma or urine porphyrins
   - **Erythropoetic:** get aneamia, non-immune hydropes & hyperbilirubineamia in early infancy and non blistering photosensitivity after sun exposure in early childhood. Screeining: erythrocytes or plasma porphyrins

Causes and types of peripheral neuropathies (modified from Forfar p898)

<table>
<tr>
<td>Nutritional & metabolic neuropathies
• Diabetes
• Thiamnine deficiency
• Pyridoxine deficiency
• Renal failure</td>
<td>Inflammatory neuropathies
○ GBS
○ Chronic inflammatory demylination neuropathy
○ Vasculitic neuropathy
○ Leprosy
○ Sarcoidosis</td>
</tr>
<tr>
<td rowspan="2">Hereditory neuropathies
• Leukodystrophy
• Hereditary sensory neuropathies
• Hereditary motor and sensory neuropathies
○ Charcot-Marie-Tooth disease
○ Refsum dx
○ Dejerine-Sottas dx</td>
<td>Toxic neuropathies
• Lead
• Arsenic
• Vincristine
• Organic solvents</td>
</tr>
<tr>
<td>Miscellaneous
• Amyloid neuropathy
• Paraneoplastic neuropathies
Neuropathies associated with immunoglobulin abnormalities</td>
</tr>
</table>

Neuro tutorial: Weakness of lower limbs: 10.05.2001, B1E

Possibele causes:

- Autoimmune: GBS – post infectious.
- Drugs: D4T, INH
- HIV associated
- Leprosy (sensory)
- Metabolic: mitochondrial, metachromatic leukodystrophy
- Genetic causes
- TB myelitis
- Viral radiculopathy (CMV, EBV, herpes, varicella)

Diagnosis:

- Nerve conduction study (for prognostic purpose)
- Axonal – abnormally delayed due to demylination
- LP: Increased CSF proteins due to demylination
- MRI
- CK to exclude muscle problem
- Infectious markers: CMV, EBV, herpes, varicella

Treatment:

Life threatening (when there is involvement of bulber, respiratory or autonomic nerves)

- Immunoglobulines: 1g/kg for 2 days to:
    - Neutralize antibodies
    - Reduce duration of acute phase
    - Reduce need for ventilation

Interemediate:

- Splintage
- Sore prevention
- Notify
- Tegretal for neuropathic pain
- Bladder care – prevent neuropathic bladder
- Neutrition

Exam question:

If nerve conduction is normal & CSF has normal findings, what are the causes?

- Chronic infections
- HIV
- Genetic causes

DEGENERATIVE BRAIN DISORDERS

DBD is characterized by progressive loss of previously acquired intellectual motor or sensory function. Three groups with 2 subsets:

1. **Grey matter:** with neuronal storage or without, present with seizures, dementias and decreased alertness
2. **White matter:** neurodegeneration – neurodystrophies or dymelinating, present with spasticity, hyper-reflexia and visual abnormalities
3. **Cerebellar:** truncal ataxia, nystagmus and hypotonia
4. **Basal ganglia dx**: movement disorders
5. **Brain stem**: abnormal extraocular movements and respiratory symptoms
6. **Spinal cord**: paraplegia

- **Cherry red spots:** found in Tay Sachs, Niemann Pick and MLD
- **Kayser Fleisher rings:** unilateral or bilateral, complete or incomplete, golden brown or grayish green rings at limbus of cornea usually at 12/6 o-clock position. May present with hepatitis dx. Always present in pts with neurological findings. Also seen in familial cholestatic syndrome and CAH with cirrhosis.
- **Differential diagnosis of degenerative brain disorders:**
  - Chronic epilepsy and CP
  - Lead poisoning
  - Infections like syphilis, rubella, HIV
  - Hypothyroidism
  - Structural brain disorder
  - Vitamin deficiencies

GREY MATTER	
WITH NEURONAL STORAGE	**NO NEURONAL STORAGE**
1. Ganglioside storage: Tay Sachs: normal neurodev in 1st few months. Then hyperaccusis, listlessness, irritability, hypotonia, seizures, devt, regression, cherry red spot in macula **2. Sphingolipids other than gangliosides** • **Infantile Gaucher's type 2**: HSM, FTT • **N-pick:** Early infancy with HSM, Jaundice, cessation of development, MR, cherry red spots on macula. BM – foam cells • **Fabrys**: AR, subcut nodules, arthropathy, hoarseness, poor growth and development, death within 2 yrs 3. **Other:** GSD II – symmetrical muscle weakness, macroglossia, cardiomegaly, FTT. Poor prognosis. Death within 1 yr	**1. Alpers:** Recurrent seizures and dementia. Early infancy and childhood **2. Leigh:** AR. Presents in infancy. Stupor, development arrest, loss of vision, dementia, vomiting, wt loss, weakness, seizures, spasticity and flaccidity, exacerbations and remissions **3. Menkes kinky hair:** XLR. Presents at birth – poor wt gain, hypothermia, brittle hair, seizures, development retardation, myoclonic jerks assoc with low serum Cu **4. SSPE:** 7-14 yrs. Progressive deterioration in cerebral fxn / personality changes, emotional lability, dementia, seizures, rigidity

WHITE MATTER DISEASE /SOAP	
LEUKODYSTROPHIES	**DYMELINATING**
1. MLD – aryl sulfatase def, 4 varieties: • Commonest: Infantile presents in 2nd yr of life with impaired motor fxn and genu recurvatum • Juvenile: Ataxia at 5-20 years • Fundi: Macular degen with OA and cherry red spot. Poor prog. MRI/CT for diag. **2. Adreno LD** **3. Krabbles:** Presents before 6 months – irritability, increased temp, developemental arrst. Decerebrate posture, OA, seizures **4. Sudanophilic LD**: AR. Early infancy – poor head control, rigid, macrceph, increased reflexes. Death within 5 yrs	**1. Sulders:** Early childhood cortical blindness, optic neuritis, spastic hemi/paraparesis, aphasia, seizures, dementia and coma **2. MS** **3. Devics**: Demyelination of subcutaneous and optic nerves: **Acute:** Eye pain, fever, back pain, nuchal rigidity, spinal shock, hence UMNL ± sensory level. CSF pleiocytosis. Dexamethasone for acute episodes

Symptomatic approach to CNS degenerate disease (B Nelson p866)

Grey matter degenerative diseases with visceromegaly

- Mucopolysaccharoidosis
- Neimann-Pick dx
- Gaucher's dx (infentile form)

Grey matter degenerative dx without visceromegaly

- Tay-Sach's dx
- Rett syndrome
- Neuronal c lipofuscinosis
- Mitochondrial dxs (MELAS, MERRF, NARP)

Degenerative dxs of white matter

- Metachromatic leukodystrophy
- Krabbes dx
- Adrenoleukodystrophy

Systems degeneration

- Friedreich ataxia
- Ataxia-telangiectasia
- Lesch-Nyhan syndrome
- Wilson's dx
- Leigh dx

GREY MATTER DEGERNERATION

Characterized by seizures and loss of intellectual function

A. NEUROLOGICAL STORAGE DISEASES

1. Ganglioside storage dx

Tay Sachs: Normal development for the first few months followed by hyperacusis, listlessness, irritability and hypotonia, seizures and developmental regression. Cherry red spot on macula. Increased in Jews

2. Storage dx with accumulation of sphingolipids other than ganglioside

Infantile Gauchers type II: Due to defient cerebroceramide – measured in leukocytes. Presents with FTT, bulbar palsy, hepatoslenomegaly, developmental regression, spastic quadraparesis and bone pain with typical X-ray findings. Bone marrow – crumpled tissue paper appearance

Niemann pick: Presents in early infancy with jaundice, hepatoslenomegaly, cessation of development and mental retardation. Cherry red spot in macula. Bone marrow – cells are vacuolated – appear like foam cells, not tissue paper appearance

Fabreys dx – AR. Present with subcutaneous nodules, arthropathy, hoarseness, poor growth and development. Death occurs within 2 yrs of respiratory infections and malnutrition

3. Other neurological storage dx:

Glycogen storage dx, pompes type II: Lethal - affects all muscles and nerve cells. Presents with symmetrical muscle weakness, macroglossia, cardiomegaly and failure to thrive. Prognosis very poor with death <1 yr

B. DEGENERATION OF GREY MATTER WITHOUT NEURONAL STORAGE

1. **Alpers dx:** Presents in early infancy and childhood with recurrent seizures and dementia
2. **Leigh dx:** AR. Presents in infancy with stupor, development arrest, loss of vision, dementia, vomiting. Weight loss, weakness and seizures. Spasticity and flaccidity. Course follows exacerbations and remissions
3. **Menkes Kinky Hair dx**: X-linked recessive. Presents at birth with poor weight gain, hypothermia, sepsis, brittle hair, followed by developmental retardation, seizures and myoclonic jerks. Death occurs in <1 yr associated with low serum copper
4. **SSPE:** Occurs 7 years following measles infection. Peak age: 7-14 yrs. Presents with progressive decline in cerebral function. Personality changes and emotional lability, myoclonic jerks or grand mal seizures, dementia and rigidity. CSF shows increased gamma globulin level and high measles antibody titres > 1:128. EEG shows repeated bursts of generalized high voltage slow wave complexes. May also be caused by herpes simplex encephailitis – get lateralised periodic epilepsy. Fatal within 2 yrs

WHITE MATTER DEGENERATIION

Characterized by Spasticity, Optic atrophy, Ataxia, Peripheral neuropathy (SOAP)

A. THE LEUKODYSTROPHIES

1. **Metachromatic leukodystrophy** Due to aryl sulfatase deficiency. There are 4 clinical variants – 3 have a variable age of onset and 1 juvenile.
   - The late infantile type: Most common – present in 2nd year of life with impaired motor function and genu recurvatu.
   - Juvenile type presents between 5-20yrs with ataxia and intellectual deterioration.
   - Adult type presents after age 20 yrs with weakness, dementia, pyschosis. Usually normal development till age 12-14 months, followed by gait disturbances, ataxia, seizures, bulbar signs, intellectual regression, areflexia especially ankle, peripheral neuropathy, terminal rigidity, blindness and deafness. Fundoscopy shows macular degeneration, cherry red spot and optic atrophy. CSF – increased proteins. Progressive – poor prognosis. Screening test – Metachromatic material in urine. (toludine blue); MRI/CT scan; Prenatal diagnosis: Aryl sulfatase A in culture cells, skin fibroblasts
2. **Adrenal leukodystrophy**: Perioxisomal disorder with hyperpigmentation
3. **Krabbe dx:** Presents before 6 months with irritability, unexplained fever, and developmental arrest with milestone regression, decerebrate posturing, optic atrophy and seizures. CSF protein elevated
4. **Sudanophilic leukodystrophy:** AR. Presents in early infancy with poor head control, rigidity, hyperreflexia, macrocephaly. Death occurs within 5 yrs

B. DEMYLINATING DISEASE

1. **Sulders dx:** Presnts in early childhood with cortical blindness, deafness and optic neuritis, spastic hemiplegia and paraparesis, aphasia and seizures, dementia and coma
2. **Multiple sclerosis:** 1% occurs in children < 15 yrs. Course follows remissions and exacerbations get cerebellar ataxia, spastic weakness, retrobulbar optic neuritis, and diplopia. May be acute or subacute. Diagnosis mady be multiple neurological deficits and relapsing course. CSF pleocytosis and oligolonal bands. Treatment: ACTH during exacerbations
3. **Neuromyelitis optica:** (Devics dx): Demyelination of subcutaneous and optic nerves. Acute attack usually presnts with eye pain/fever/back pain/nuchal rigidity. Iinitial spinal shock may be followed by UMN signs. Sensory level may be presnt. CSF shows pleocytosis. Treatment: Dexamethasone in acute episodes

SYSTEMS DEGENERATION

A. SPINOCEREBELLAR DISEASE

1. **Frederich's ataxia:** AR. Presents bewteen 5-14 yrs with staggering gait, clumsiness in writing, nystagmus, dysarthria, kyphoscoliosis, pes cavus, loss of vibration and position sense, areflexia and cardiomyopathy
2. **Ataxia telangiectasia:** Presents in early ingancy with ataxia, B & T cell dysfunction, impaired CMI, occulomotor apraxia, recurrent sino-pulmonary infection, telangiectasia of skin and conjunctiva and increased incidence of malignancy. IgA & IgE are deficient
3. **Refsums dx:** AR. Present between age 4-7 yrs with neuropathy, retinitis, blindness, icthyosis, due to phytanic acid deficiency. Treatment: Phytol free diet
4. **Bassen Kornzweig syndrome** (abetalipoproteinaemia)
   Begins in childhood with steatorrhoea and FTT and Ataxia, retinitis pignmentosa, peripheral neuritis, abnormalities in position and vibration sense, muscle weakness and mental retardation

B. BASAL GANGLIA DEGENERATIONS

1. **Wilsons dx**: AR. Presents in infancy or adulthood, due to caeruloplasmin deficiency (levels <10micrograms per dl) resulting in normal or increased copper levels (>250micrograms/dl) and increased urinary copper (40-100 micrograms/day), presents with wing beating tremor, dystonia, athetosis, degenerative changes in brain (gliosis, neuronal degeneration in basal ganglia esp putamen but also in cerebral cortex and frontal lobes), cavitation, cirrhosis, KF rings in cornea. Younger patients have increased hepatic involvement whilst age >20 yrs increased neurological signs. Hepatic dx may present with asymptomatic slenomegaly, subacute/CAH/ fulminant hepatic failure, crytogenic cirrhosis. CNS/ psychiatric changes present with intention tremor, dysarthria, dystonia, deterioration in school performance, behavioural changes and KF rings. Renal presentations include Fanconi syndrome, progressive renal failures with alteration in tubular transport of amino acid, glucose and uric acid. Arthritis and endocrinopathies may occur. Treatmen: Copper chelating agents - penicillamine (S/E: hypersensitivity, interaction with collagen and elastin, zinc def, aplastic aneamia). Add vit B6 to diet and vit K. Restrict copper intake to 1mg/day. Avoid nuts, chocolates, liver and fish.
2. **Dystonia musculorum deformans**: Also called torsion dystonia, AD/AR – increased in Ashkenazi Jews. Gets generalized dystonia which begins in childhood and becomes progressively worse →leaves individuals seriously disabled and confine to a wheelchair. Abnormal posture, eyelid spasm, torticollis, scolsiosis, lordosis, kyphosis, facial grimacing, tremors and speaking difficulties
3. **Juvenile Huntington's dx**
   Pts may become coarse, irritable and aggressive and dpresent with chorea which greadually worsens as the dx progresses and affects walking and speech. Dementia, akinesia and rigidity may develop

CARDIOLOGY

CYANOTIC CONGENITAL HEART DISAESE

Cuases of central cyanosis:

• CNS depression	Pulmonary disease	Cardiac disease
• Perinatal hypoxia	• HMD	• Cyanotic CHD
• Heavy metal sedation	• Pneumothorax	
• Intrauterine foetal distress	• Pleural effusion	
	• Diaphragmatic hernia	
	• PPHN	

List of cyanotic congenital heart defects

1. TOF
2. TA
3. PA with intact VS
4. TGA
5. Ebstein anomaly
6. DORV
7. Single V
8. Hypoplastic left heart syndrome
9. Truncus arteriosus
10. TAPVR
11. Hetrotaxia – atrial isomerism
12. Eisenmanger's

Common mixers (CCF with cyanosis)

1. TGA –VSD
2. TAPVC (splitting of second heart souns)
3. Common atrium
4. Single ventricle
5. Tricuspid atresia – bounding pulses + click

Syndromes with cyanotic heart lesions

1. Di George → TOF
2. Foetal alcohol → TOF
3. Goldenhars → TOF
4. Foetal warfarin→ TOF
5. CHARGE → TOF
6. Carpenter →TGA
7. Infant of diabeteic mother → TGA
8. Velocardiofacial → TGA
9. Marfan →MR, AR, aortic aneurysm
10. Williams

Hyperoxia test

It is used to distinguish cardiac from respiratory causes of cyanosis

Principle:

- If there is right to left shunt in CCHD no amount of oxygen in pulmonary circulation will alter the desaturating effect of the shunt
- If there is pulmonary defects causing cyanosis this may be corrected by increasing inspiratory O_2

Procedure:

- Place infant in 100% oxygen for 10 minutes. If infant remains cyanotic after this period, cyanosis is said to be due to cyanotic CHD
- This can be defined in blood gas as follows:
    - Arterial blood O_2 <20 kpa → cyanotic CHD
    - Arterial O_2 <27 kpa but >20 kpa → equivocal
    - Arterial blood O_2 → > 27kpa → respiratory disease
- Exceptions to this rule are:
- Sever respiratory dx may result in persistant cyanosis even in 100% inspired oxygen
- It is not contraindicated in duct dependent lesions
- Some clonicians prefer not to have this text or to have prostacyclin E2 to hand to reopen a duct if needed

Classification of cyanotic defects: (Parks p76)

Increased pulmonary blood flow	
LVH or BVH	**RVH**
• Persistant truncus arteriosus type 1 • Single ventricle without PS • TGA +VSD • Polysplenic syndrome	• TGA • TAPVR with obstruction • HLHS • Subaortic DORV without PS

Decreased pulmonary blood flow		
BVH	**LVH**	**LVH**
• TGA +PS • Persistant truncus arteriosis with hypoplastic PA II & III • Single venricle with PS	• Tricuspid atresia • Pulmonary atresia with hypoplastic RV	• TOF • PVOD (seconday L-R shunt • Ebstein's anomaly (RBBB) • Asplbnic syndrome • SA DORV with PS

SHORT NOTES

1. FALLOTS TETRALOGY (Parks p239)

- Has 4 components:
  - Non-restrictive VSD (perimembranous)
  - Right ventrical outlet tract obstruction
  - Over-riding of aorta
  - RVH
- Defect embryology → hypoplasia of conus
- Severe infundibular PS and the state of anaemia

Clinical examination:

- Cyanosis, clubbing and polycythaemia
- ESM (3-5/6) along LSB and single S2, ejection click, systolic thrill (50%)
- Dyspnea on exertion
- Prefers squatting position during hypoxic spell
- May be acyanotic depending on progression of the infundibular PS and the state of the anaemia
- 25% have a right sided aortic arch. 2% have complete AVSD (Downs)
- 5% have abnormal coronary arteries – anterior descending branch arising from RCA
- **CXR** – boot shaped heart, decreased pulmonary bay, RVH, oligaemic lung fields, uptilted apex, concave PA segnment and right atrial enlargement (25%)
- **ECG** – right axis deviation and RVH in cyanotic TOF. Normal axis and BVH may be seen in acyanotic form
- **Echo and doppler studies**

- No CCF – if patient presents in CCF – exclude anaemia, mycarditis, IEC, CMO AI and post shunts
- **Look for complications** – cerebral venous thrombosis <2yrs, brain abscess >2 yrs, infective endocarditis (rare), hypoxic spells
- **Management**
  - Surgery
    - *Palliative* – Blalock Taussig shunt right subclavian A & ipsilateral right PA, Waterston shunt, Potts operation. With successful shunts get diminished cyanosis and machinery murmur
    - *Corective surgery* – infundibulectomy to relieve RVOTO, patched closure of VSD, time to operate:
      - age <2yrs → mortality 5%;
      - age >2 yrs →10% mortality,
    - Timing is controversial. With 2 stage repair (shunt then correction) mortality →5%, early repair may laed to RV dysfunction, follow up essential
- **Management of cyanotic spells** – position (squat/knee chest), MRL polus, morphine 0.2 mg/kg subcut/imi, correct metabolic acidosis, give 100% oxygen, prophylactic propranolol (0.01-0.25mg/kg oral /ivi) and Fe supplements. Phenylephrine 0.02 mg/kg ivi (increases systemic arteria pressure), Ketamine 1-3 mg/kg/dose (increases peripheral resistance and sedates infants)

2. TRISCUPID ATRESIA

- Must have shunt VSD/PDA/ASD to survive
- LVH/LAD and oligaemic lung fields
- Murmurs depend on shunt
- More common than hypoplastic RV with pulmonary atresia
- RV is hypoplastic (poor RV forces on ECG), differential diagnosis→ECD - but ECD is associated with RVH
- Triscuspid atresia (without TGA) – VSD is always present (all pulmonary blood flow must pass through it). With age VSD tends to get smaller, leading to diminished blood flow
- **Clinical features:**
  - Cardinal features →cyanosis + LVH + LAD, continuous murmur of PDA or 2-3/6 holosystolic/early systolic murmur depending on shunt, S2 single, hepatomegay
  - Other clinical features depend on size of VSD and PBF. If duct closes – get marked hypoxaemia. When VSD's are large pts do well (<1 yr olds). Infants with small VSD's have CXR with normal heart and decreased PBF
- **ECG:**
  - Superior QRS axis. LVH due to hypoplastic RV and increased volume of work of L ventricle. Gets marked RAE (increased P wave amplitude) and LAD
  - Left bundle branch (abnormal conduction) results in superior vector. At 2-3 yrs get inverted T waves in L precordial leads and severe LVH with fibrosis

- **CXR:** minimal cardiac enlargement, reduced PV markings and concave main PA segment
- **Treatment and prognosis:** in the newborn – prostaglandin infusion to maintain open duct until BT shunt performed. If VSD is good size or arterial sats >75%, administering PGE is not necessary. If CCF occurs in 1st month of life – use anti congestive measures. For physiological repair PVR must be low; pulmonary veins and arteries must not be badly disordered and good size and LV compliance must be low. Rashkind procedure – Baloon atrial septostomy to improve RA to LA shunt if ASD small
- **Modified Fontans procedure**: corrective surgery – close atrial septum, right atrial appendage attached to PA or RV outflow tract. If anatomy of right atrium is not satisfactory, a conduit is placed. Surgery is rarely successful in patients less than 1 year and is best at 3-4 yrs (opposite to Fallots). Operative risk is 10%
- **Complications** are large congested livers and sick sinus syndrome

3. PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

- Pulmonary atresia
  - 80% pulmonary valve atretic
  - 20% infundibulum atretic
- Main PA varies in size
- High pressure in ventricles is decompressed by dilated coronary microcirculation – coronary sinusoids
- Condition is associated with important anomalies of coronary As
- RV shows varying degrees of ischaemia, infarction, fibrosis, endocardial fibroelastosis
- Interatrial communication is needed – ASD, PFO and PDA or collateral arteries
- Sever cyanosis, S2 single, heart murmur may be absent and may be present if TR or PDA
- **ECG:** QRS axis normal, in contrast to TA where it is superiorly oriented
- **CXR:** RA enlargement
- **Treatment:** PGE_1, cardiac catheterisation, pulmonary valvotomy with balloon pulmonary valvoplasty

4. TRANSPOSITION OF GREAT ARTERIS

- *Cardinal features:* Presents at birth, S2 single, later get increased P2 as pulmonary hypertension increases, ESM LSB. May or may not get associated PS. With PS, lung fields are oligaemic. Without PS lung fields are plethoric
- Immediate treatment → Rashkinds (artificial shunt)

- Definitive management → Mustard/Sennigs (atrial) at foramen ovale (intra-atrial baffle), or Jaytene (arterial switch operation with coronary reimplantation). Post-op 10% get pulmonary stenosis
- **General points about TGA** – is the most common cyanotic condition in newborn period. Vessels arise from the inappropriate ventricle. Survival depends upon mixing of blood between the two circulations. Associated abnormalities – may

have common carotid arteries/AV valves – poor prognosis with 30-50% abnormality

TYPES OF TGA

4.1 D-TGA with intact ventricular septum

- The most common variant
- Presents with severe hypoxaemia, acidosis and death. Cyanosis occurs in 1st day of life and increases as the duct closes. Examination may be normal or with a 2/6 esm. CXR may be normal or mildly increased PBF. Egg shaped heart, ECG normal
- **Cardiac catherization** shows RV pressures at systemic level, it is the only congenital cardia lesion where the LV pressure is less than the aortic pressure

- **Treatment:** medical emeregency. Treat with prostaglandin infusion – maintains patency of PDA. Immediate palliation → Rashkind shunt in patient with intact ventricular septum – get improved oxygenation and decreased interatrial pressure gradient. This decreases the hypoxia and cyanosis

4.2 TGA with VSD

- Cyanosis is not a major problem
- Presents with CCF after a few weeks of life
- **Clinical examination** shows hyperdynamic heart with prominent R & L ventricle impulses. Single S2. Look for features of pulm HT (palpable or loud P2). Murmur grade 3/6 or more
- CXR shows increased heart size with increased PBF
- ECG shows biventricular hypertrophy or pure RVH
- **Treatment for CCF** – digoxin, diuretics, increased caloric density. Correct anaemia. Do Mustards/ Sennigs with closure of VSD, Jaytenne - arterial switch, VSD closure and coronary re-implantation
- **Complications** - Baffle obstruct, atrial arrthymmias, RV dysfunction or Triscuspid regurgitation
- Best operation results if done at birth

5. EBSTEIN'S ANOMALY

- Downward displacement of tricuspid valve forming 3 separate chambers on the right side of the heart
- **Cardinal features** – cyanosis and massive cardiomegaly due to sever tricuspid incompitance and a huge R atrium
- Arrthymmias, widely split S2 with 3rd and 4th HS (i.e. quadruple rhythm)
- It is the only cyanotic heart condition with a big heart
- Presents at birth
- Associated with RHF and R-L shunt through foramen ovale
- May be associated with WPW syndrome
- Some pts may be mildly symptomatic and cyanotic – some are diagnosed incidentally later on in childhood with SVT's

- Most have cyanosis and clubbing

- **ECG** – RVH; RAH, RBBB and Bizarre QRS complexes
- **CXR** – massive cardiomegaly with right atrial prominence (balloon shaped heart + decreased PV markings). During cardiac caths, may have episodes of SVT
- **Echo**: exaggerated displacement of septal leaflets of T Valve insertion on ventricular septum
- Prognosis is guarded. Transplant needed
- Medical treatment:
- Mechanical ventilation, PGE1 infusion, ionotropic agents. Treat metabolic acodosis. Treat SVT → Adenosin, propranolol, dental hygein, activity restriction
- Surgical: Danielson technique for tricuspid repair

6. DOUBLE OUTLET RT VENTRICLE (Parks p289)

- Both aorta and PA arise from RV – only outlet for LV is VSD
- Great arteries lie side by side – Aorta right, PA left
- Position of VSD & presence of or absence of PS → influence hemodynamics

TYPES

Subaortic VSD without PS
- Oxygenated blood from LV → aorta & desaturated from RV to PA
- Mild or no cyanosis
- Resembles VSD with PHTN & CHF → growth retardation and tachypnoea
- Hyperactive pericardium, lod S2, holosystolic or early systolic murmur
- ECG like CECD → superior QRS complexes (-30 to -170^{O})
- CXR: cardiomegaly + increased PV markings

Subaortic VSD with pulm stenosis (Fallot type)
- Some desaturated blood goes to aorta
- Cyanosis → reduced PBF (clinical picture of TOF)
- Growth retardation + cyanosis
- ECG: 1st degree AV- block
- CXR: normal heart size, reduced PV markings

Sub pulm VSD (Tussig Bing Syndrome)
- Oxygenated blood directed to PA & desaturated to aorta
- Clinical picture like – TGA. PBF increases with fall in PVR
- ECG: RAD, RAH, RVH
- CXR: cardiomegaly, increased PV markings, prominent PA segment

7. SINGLE VENTRICLE

- No progression or QRS complexes
- Depends upon pulmonary blood flow
- With increased PBF or decreased PBF
- Early cyanosis may occur
- ECG: abnormal Q waves, 1st or second degree heart block, arrythemias
- Echo: diagnostic → 2 AV valves in single ventricle

8. HYPOPLASTIC LEFT HEART SYNDROME

- Cyanosis and CCF within the first 24 hrs of life + high prevalance of neurodevelopmental abnormalities and dysmorphism
- Increased pulmonary vascular markings (pulm oedema)
- All peripheral pulses are weak or absent due to inadequate maintainance of systemic circulation - may get pulmonary hypertension
- Skin → grayish blue colour with poor perfusion
- Cardiomegaly – CCF with hepatomegaly + gallop rhythm
- ECG: RVH
- Echo → diagnostic = LV cavity diminutive – RV cavity markedly dilated with large TV
- Treatment: PGE1, ventilation, balloon atrial septostomy
- Surgery: Norwood operation (Parks p272)
- Prognosis → poor

9. TRUNCUS ATERIOSUS

- Single arterial trunk with/without VSD
- Sats in arota and pulmonary artery are equal
- Very wide pulse pressures (collapsing pulse)
- **Clinical examination** – hyperdynamic heart; loud 1st and 2nd HS and aortic ejection click. Harsh regurgitant SM 2-3/6 ULSB with/without a VSD murmur
- If pulm vascular R is increased gets progressive cyanosis, polycytheamia and clubbing
- **CXR:** increased CTR – plethoric lungs - 30% have right aortic arch and associated with Di George (exclude hypocalcaemia and T cell deficiency)
- ECG: usually Biventricular H, LAH, normal QRS-axis)
- Treatment: anticongestive measures, digitalis, diuretics, check serum Ca, Mg and supplement prn. Prophylaxis against pneumo + strepto
- No immunization with live cvaccines
- Irradiated blood products for transfusion
- Rastelli procedure at 3/12 → Conduit with later revision

10. TAPVR

- **Types:** supradiaphragmatic and infradiaphragmatic
- Present with CCF and severe pulmonary congestion
- Infradiaphragmatic type associated with onset of pulm HT within 1 month

NB! Two *cyanotic conditions with widely split S2*
Ebsteins & TAPVR (no/mild obstructive type)

1. Obstructive veins

- Newborn with severe cyanosis and tachypnoea, no murmurs
- ECG – RVH
- CXR – normal heart

2. Mild/no obstruction

- Presents after the newborn period with subtle cyanosis which increases with crying and exercise
- CCF: severe hyperactive R ventricle. Widely split S2
- ECG: severe RVH
- CXR: increased CTR and plethora
- Rarely asymptomatic – resembles simple large ASD
- **Investigations:**
- **CXR:** snowman appearance/figure of 8
- **Echo**: common pulmonary venous return
- **Cardiac cath:** common mixing at R atrial level with equal saturation – R atrium and ventricle and pulmonary artery and L atrium LV and arota
- **Management:** surgical emergency if newborn has obstruction. MR in 10-25% of these newborns and 2% in others

NB: widely split S2 →TAPVR and ebsteins
Loud S1 & S2 → truncus arteriosus

11. HATEROTAXIA – ATRIAL ISOMERISM – SPLEMIC SYNDROMES

Failure to differentiate into Rt sided and Lt sided organs

1. Rt sided isomerism – Rt atrial isomerism – Asplenic syndrome – Ivemark's syndrome [absence of spleen – tendancy of bilateral right sidednees]
2. Lt atrial isomerism – polysplenic syndrome [multiple splenic tissues – tendancy of bilateral left sidedness]

Significant differential power

- IVC almost always normal – asplenic syndrome [superior QRS axis]
- IVC-intrupted with azygus continuation – polysplenia
- CVS abnormalities are sever in asplenia – than those with polysplenia
- Non cardiac findings – suggesting hetrotaxia
- Symmetrical midline liver – palpation or CXR

- Discordant apax beat and stomach bubble on CXR
- Bilaterial atresia in the neonate with CHD
- Symmetric main stem bronchi on CXR
- Superior P axis on ECG

12. EISENMENGERS

- Syndrome refers to reversed or bidirectional shunt through VSD due to pulmonary vascular obstructive dx (PVOD). Also occurs with ASD, AVSD, PDA and other communication between aorta and pulmonary artery
- Isolated ASD with PVOD is rare
- In E, PVR remains high due to prolonged elevated pulmonary pressure in severe obliterative intimal lesions in these vessels. Pulm vasc dx is more often due to high pulm resistance than increased pulmonary blood flow
- **Clinical features:** symptoms usually in 2nd and 3rd decade. Gets R-L shunting when pulm resistance exceeds systemic resistance. Cyanosis, dyspnea, chest pain, syncope and heamoptysis.
- Clinical examination shows RV heave with loud narrowly split S2 and usually soft esm at LSB. P2 palpable at ULSB. Degree of cyanosis depends on stage of dx
- May get functional P1with diastolic murmur LSB (Graham Steele murmur)
- **Diagnosis:**
  - FBC: polycythaemia.
  - CXR: usually normal to cardiomegaly. MPA prominent. Prominent vessels in hilar areas (peripheral pruning). Prominent RV and RA.
  - ECG: RVH and tall/spiked P waves look at lead II
  - Echo shows thick RV wall; communication between pulm and systemic circulations; increased ratio of pre-ejection period to ejection period
  - **Cardiac cath** shows bidirectional shunt at defect, equal systemic pressures and pulm pressures. Normal pulm capillary wedge pressure(rules out LVOTO) and decreased aterial O2 sats
- **Management**: prevention by surgical elimination of large intra cardiac or great vessel communication during infancy. Symptomatic management of polycythaemia with venesection and volume replacement
- *Must rule out respiratory tract pathology for pulmonary HTN*

OBSTRUCTIVE LESIONS

Right sided →PS
Left sided →valvular and coarctation of aorta

1. PULMONARY STENOSIS

- PS may be valvular, subvalvular and supravalvular
- Dysplastic P valves are seen in Noonan's syndrome
- PS mild → asymptomatic
- Moderately sever → exertional dyspnea, easy fatiguability, CHF with hepatomegaly or exertional chest pain
- Newborn with critical PS may present with poor feeding, tachypnoea and cyanosis
- Syst ejection click at ULSB & S2 may split
- **ECG:**
  - Mild cases: normal
  - Moderate: RAD & RVH
  - Nenate may show : LVH
- CXR: usually normal heart size. Prominent PA seg in sever cases due to post puln stenosis dilatation
- Pulm vaccular markings normal or reduced
- Neonate: oligaemic lungs with varying degrees of cardiomegaly

Treatment:

- Neonates: PGE1 infusion
- Balloon valvoplasty
- Antibiotic prophylaxis for SBE

2. AORTIC STENOSIS

- Supravalvular, valvular or subaortic valve stenosis
- Clinical manifestations
- New borns with critical PS → Respiratory distress, hypoperefusion with weak and thread pulses, pale pool skin and slow capillary refill time triggered by ductal constriction.
- Exertional chest pain, easy fatiguability or syncope
- Acynotic may develop normaly
- Narrow pulse pressure
- Systolic thrill palpable ULSB
- Harsh 2-4/6 mid diast murmur 2^{nd} Lt or Rt intercostal space radiate to neck/apex
- Elfin facies, mental retardation, friendly cocktail party personalities → supra valvular AS e.g., Williams' syndrome
- **ECG:** mild cases → N, sever cases → LVH
- **CXR:** post stenotic aortic dilataion → prominent aortic knob, generalized cardiomegaly and pulmonary venous congestion

- **Treatment**

- Stabilization with ionotopes and diuretics to treat CHFand PGE1 infusion to reopen the ductus
- Mechanical ventilation may be useful
- Balloon valvuloplast percutaneous balloon valvuloplasty is now regarded as the first step in managing symptomatic neonates
- Surgery – closed aortic valvotomy, Norwood procedure or Fontan operation

3. COARCTATION OF AORTA (Fig see Parks p207)

Symptomatic infant

- Poor feeding, dyspnea, poor wt gain
- Acute circulatory shock and varying degrees of respiratory distress
- Pale, anuria, oliguria and sever academia
- Cyanosis of half the body
- Peripheral pulses – wk and thready as a result of CHF
- BP differential: usually right arm BP >left arm and upper limb BP>LL
- ESM (50% cases)

Asymptomatic infant

- Arterial pulses are weak or absent in legs
- Hypertension in arms and BP in legs equal or lower than arms
- Systolic thrill @ suprasternal notch
- ESM 2-4/6 URSB. Leftward QRS complex, LVH

General features

- Simple coarct occurs at level of ductus arteriosus or just below origin of left subclavian artery, no obstruction to flow and usually missed at birth
- ECG – pure RVH followed later by LVH
- Echo may miss the diagnosis.
- CXR – rib notching after 5 yrs and Barium swallow → E- Sign
- Treatment – operate at 4 yrs age
- If BP >160 justified to operate at 2 yrs age, use aortic graft/subclavian flap/angioplasty
- Complicated COA →associated with PDA/VSD → results in CCF in the 1st weeks of life – emergency operation needed
- Re-stenosis may occur post-op
- Spinal cord ischaemia may occur
- New recommendations – balloon valvuloplasty in re-coarctation
- If complex mortality 10-20%
- Aortic angioplasty may be used for aortic narrowing/re-coarctation

4. INTRUPTED AORTIC ARCH

Aortic arch atretic or segment of the arch is absent

- **Types:**
  - Type A: intruption distal to Lt subcl A
  - Type B: intruption between Lt carotid & Lt subcl A. Gi-George synd is reported in 50% of pts with this type
  - Type C: intruption between innominate & Lt carotid As
- IOA is usually associated with PDA & VSD and sometimes with bicuspid aortic valve, mitral valve deformity, PTA or subaortic stenosis
- Resp distress, variable degrees of cyanosis, poor periph pulses and signs of CHF or circulatory shock develop during 1st few days
- **CXR:** cardiomegaly, increased pulm vasc markings, pulm oedema or pulm venous congestion. Upper mediastinum may be narrow (absence of thymus)
- **Treatment:**
  - PGE1 infusion, work up for Di-George syndrome (serum calcium)
  - Citerated blood be avoided for transfusion in Di-George & irradiated blood be used

Surgical repair of intruption and VSD

ACYANOTIC HEART DIASESE

Classification (Parks p75)

Incraesed pulmonary blood flow		Normal pulmonary blood flow	
LVH or BVH	**RVH**	**LVH**	**RVH**
VSD	ASD (after RBBB)	AS OR AR	Ps
PDA	PVOD sec to L-R shunt	COA	COA (in infants)
ECD	MR	Primary cardiac dx	MS
		MR	TR (RAH+RVH)

Cardiology tutorial 05/2011 (B2E)

Apparent big cardiac shadow on CXR

- Ebstein anomaly
- Large thymus
- Pericardial effusion
- Pericardial tumor

Causes of cannon wave

- Tricuspid atresia

SVT

- AV dissociation – TA
- Restrictive intraatrial communication
- Ebstein-associated with extra neuronal pathway

Large Lt Atrium

- Ebstein
- TOF
- PA

Lesions according to time of presentation

- 1st few hrs
  - HLHS
  - Pulmonary atresia
  - Aortic stenosis
  - Pulmonary stenosis
  - Aortic atresia
- 1st few days
  - TGA
  - TOF
- 1st few weeks
  - Coarctation of aorta
  - Aortic stenosis
- 1st few months
  - Left to right shunts

1. ATRIAL SEPTAL DEFECT (Parks p161)

- 3 types: sinus venosus, secundum and primum
- Asymptomatic if low velocity flow across ASD
- Secundum type is most common
- Clinical features:
- Slender body – wt <10th centile
- Hyperdynamic RV impulse at L sternal
- Widely split fixed S_2, 2-3/6 ESM
- CXR: incrased pulm vascularity, Rt atrial enlargement on PA view, obliteration of retrosternal space on lateral view, pulmo A segment is prominent
- ECG: pure RVH, RAD, RBBB with an RSR pattern in V1 is typical finding
- Surgery indicated before 7 yrs of age. If not operated, will get Eisenmengers

2. PDA

- Usually asymptomatic, male to femal ratio 3:1
- Large PDA may cause LRTIs, atelectasis, and CHF (ac by tachypnoea and poor weight gain)
- Exertional dyspnea
- Bounding peripheral pulses with wide pulse pressure (elev syst & low diast press)
- Hyperactive praecardium
- Systolic thrill LSB, P2 usually normal1-4/6 continuous (machinery) murmur @ left infraclavicular area or ULSB
- If PVOD develops R to L ductal shunt → cyanosis
- **ECG:** LVH in small and BVH in large PDA. If PVOD develops RVH
- CXR – increased pulm vascular markings, cardiomegaly of varying degrees
- If PVOD develops → normal heart size
- Echo: confirms diag
- Increased risk of PVOD and infective endocarditis compared with VSD
- Spontaneous closure of congenital PDA – small chance
- DD
  - Coronary AV fistula
  - Systemic AVfistula
  - Pulmonary AV fistula
  - Venus hum
  - Collaterals in COA
  - VSD with AR
  - Absence of PV
  - Persistant TA
  - Aortopulmonary septal defect
  - Peripheral PA stenosis
  - TAPVR
- **Treatment:**
  - Indomethacin slam chance in term infants

- Diuretics and digoxin if CCF
- No exercise restriction
- Prophylaxis for SBE is indicated
- Non-surgical closure: Amplatzer PDA device
- Surgical closure

- **Causes of narrow pulse pressure:** CS; severe AS; pericardial tamponade

3. VSD (Parks 166)

- 15-20% of all congenital heart diseases
- **Types:**
  - Membranous septum
  - Muscular septum
    - Inlet (tricuspid valve)
    - Outlet (infundibular – semilunar valves)
    - Trabecular
      - Marginal muscular
      - Central muscular
      - Apical muscular
- Large shunt VSD – symptomatic
- Systolic thrill, precordial buldge & hyperactivity
- 2-5/6 regurgitant systolic murmur (LLSB)
- ECG: small VSD → normal ECG
- Moderate → LVH, LAH
- Large: BVH with or without LAH
- CXR: Cardiomegaly of varying degrees
- PVOD – may develop → main pulmonary artery & hilar PAs enlarge but peripheral lung fields are ischemic and N heart size
- If small with normal pulm pressure – no surgical closure, if large leading to CCF or those with RVH on ECG need cardiac cath at 3/12

4. ENDOCARDIAL CUSHION DEFECT →AVSD (see fig Parks 181)

- Broad spectrum of AVSD
- Simplest → VSD in ECD position and ostium primum ASD and def of anteromedial leaflet, leading to MR. If MR severe – get early LVF
- Complete ECD – structures involved
- Ostium primum ASD
- VSD in the inlet ventricular system
- Clefts in anterior MV
- Septal leaflet of TV
- Complete type is commoner in Downs syndrome
- Features:
- Undernourished, tachycardia, tachypnoea
- Hyperactive praecardium with syst thrill @ LLSB
- S1 accentuated – S2 narrow split –P2 increase intensity

- Grade 3-4/6 holosyst murmur @ LLSB
- With complete type get severe CCF and / pulm vascular disease
- ECG – Superior QRS complex – increased PR interval → 1st deg heart block
- Early surgical repair by 3/12 age is strongly recommended, with a partial AVSD – surgery before school 3-10% hospital mortality. Unoperated – 8-16% mortality

5. PARTIAL ANAMALOUS PULMONARY VENOUS RETURN

- Types:
  - Rt PV drains in SVC with ASD
  - Rt PV drains in IVC with no ASD
  - Lt PV drains in Lt innominate vein
  - Lt PV drains into coronary sinus
- Pulm BF increased due to re-circulation of blood through lungs
- Symptoms depend upon associated ASD or without ASD
- With ASD → S2 widely split and fixed
- Without ASD → S2 normal
- 2-3/6 mid diast murmur ULSB
- ECG: RVH, RBBB or normal
- CXR: cardiomegaly with RA, RV enalgement, promi PA seg and increased pulm vascularity
- Cyanosis, exertional dyspnea, pulmonaryt infections common

CAUSES OF CARDIOMEGALY IN 1 MONTH OLD CHILD

CARDIAC

1. Volume overload

- At birth
  - Tricuspid incompetence
  - Pulmonary incompetence
  - Large systemic AV fistula
- Week 1
  - PDA
  - TAPVR

2. Obstructive lesions

- Birth
  - HLHS
- Week 1
  - TGA
- Week 1-4: (critical)
  - Aortic stenosis
  - Pulmonary stenosis
  - Aortic coarctation

3. Myocardial abn

- Myocarditis
- Trans myocardial ischaemia
- Cardiomyopathy
- Infant of diabetic mother

4. Rhythm abn

- SVT
- Atrial flutter or fibrillation
- Congenital heart block

NON CARDIAC

- Birth asphyxia
- Metabolic abn
- Severe anaemia
- Sepsis
- Overtransfusion/overhydration

CARDIOMEGALY WITHOUT HEART MURMUR (Parks p345)

Myocardial dx
- EF – 1ST 8 days of life – endocardial fibroelastosis
- Myocarditis – viral, idiopathic
- GSD – Cori's type II, Pompe

Coronary artery dx / myocardial insufficiency
- ALCAPA
- Collagen dx – periarteritis nodosa
- Kawasaki dx

Congenital hear dx with sever CHF
- CRITICAL as
- Co-arctation in infants
- Systemic AV fistula
- Ebsteins anomaly

Miscellaneous
- CHF 2ndary to resp dx (UAO, BPD)
- SVT with CHF
- Pericardial effusion
- Tumours of heart
- Sever anaemia
- Endocrine – thyrotoxicosis, pheochromocytoma
- Malnutrition – Beri-beri, kwashiorkor, carnitine def
- Muscle dystrophies
- Familial dilated cardiomyopathies
- Toxic reactions – sulfonamides, doxorubicin

APPROACH TO 1 MONTH OLD CHILD WITH CARDIOMEGALY

- Exclude hypoglyceamia / hypocalcaemia
- Was the mother diabetic
- Hx of birth asphyxia
- Baby cyanosed?
- Baby septic?
- Associated LAD or HSM?
- Pallor? (hydrops)
- Fluid overload?
- ECG
- CXR

Cyanotic

- Hyperoxia test to exclude pulm causes
- Exclude acidosis
- IV line – rehydrate
- Start PGE_1 0.05-0.1 micrograms/kg/min. Reduce to 0.05, 0.025 and 0.01 microgram/kg/min when desired effect achieved
- Watch for PGE_1 side effects → apnoea, flushing, bradycardia and hypotension
- Monitor BP and HR

Pulmonary stenosis

- PS mild → asymptomatic
- Moderately sever → exertional dyspnea, easy fatiguability, CHF with hepatomegaly or exertional chest pain
- Syst ejection click at ULSB & S2 may split
- **ECG:**
  - Mild cases: normal
  - Moderate: RAD & RVH
  - Nenate may show : LVH
- CXR: usually normal heart size. Prominent PA seg in sever cases due to post puln stenosis dilatation
- Pulm vaccular markings normal or reduced
- Balloon valvuluplasty, valvotomy

Aortic stenosis

- Exertional chest pain, easy fatiguability or syncope
- Acynotic may develop normaly
- Narrow pulse pressure
- Systolic thrill palpable ULSB
- Harsh 2-4/6 mid diast murmur 2nd Lt or Rt intercostal space radiate to neck/apex
- Elfin facies, mental retardation, friendly cocktail party personalities → supra valvular AS e.g., Williams' syndrome

- **ECG:** mild cases → N, sever cases → LVH
- **CXR:** post stenotic aortic dilataion → prominent aortic knob, generalized cardiomegaly and pulmonary venous congestion
- **Management**: anticongestive measures, laix, captopril ± PGE1, valvuloplasty in selected cases. Critical AS – urgent Sx

Co-arctation of aorta

Symptomatic infant

- Poor feeding, dyspnea, poor wt gain
- Acute circulatory shock and varying degrees of respiratory distress
- Pale, anuria, oliguria and sever academia
- Cyanosis of half the body
- Peripheral pulses – wk and thready as a result of CHF
- BP differential: usually right arm BP >left arm and upper limb BP>LL
- ESM (50% cases)

Asymptomatic infant

- Arterial pulses are weak or absent in legs
- Hypertension in arms and BP in legs equal or lower than arms
- Systolic thrill @ suprasternal notch
- ESM 2-4/6 URSB. Leftward QRS complex, LVH

ECG: pure RVH followed later by LVH
CXR: rib notching after 5 yrs and Barium swallow → E- Sign
Treatment: operate at 4 yrs age

- If BP >160 justified to operate at 2 yrs age, use aortic graft/subclavian flap/angioplasty
- New recommendations – balloon valvuloplasty in re-coarctation
- Fast acting inotropes, PGE_1, diuretics, oxygen where needed

Interrupted aortic arch

- Resp distress, variable degrees of cyanosis, poor periph pulses
- Signs of CHF or circulatory shock develop during 1st few days
- **CXR:** cardiomegaly, increased pulm vasc markings, pulm oedema or pulm venous congestion. Upper mediastinum may be narrow (absence of thymus)
- **Treatment:**
  - PGE1 infusion, intubate, oxygen
  - Work up for Di-George syndrome (serum calcium)
  - Citerated blood be avoided, irradiated blood be used
  - ECG: RVH
  - Surgical repair

Transposition of great arteries

- Cyanosis – CCF
- Loud S2. No murmurs unless VSD/PS
- Severly decreased O2 & acidosis

- CXR: high CTR, narrow sup med
- ECG: RAD, RVH
- Managemet:
  - Correct acidosis, hypoglycaemia, and hypocalcaemia, PGE1, oxygen
  - Atrila septosomy. Sx at atrial level → Senning/Mustard. At ventricular level (Rastelli) and arterial level (Switch)

Hypoplastic left heart syndrome

- Critically ill, tachycardia, tachypnoea, pulmonary crackles, poor pulses & vasoconstricted peripheries
- Loud S2,1-3/6 ESM
- Acidosis with slightly low O2
- CXR: mild pul oedema, high CTR
- ECG: RVH
- **Management:**
  - Intubate, correct acidosis. PGE1
  - Atrial septotostomy - Norwood then Fontan
  - Cardiac transplant → Rx of choice.

Transient myocardial ischeamia

- May lead to TTN (mild LV dysfunction)
- Transient TI/MR (papillary muscle infarction)
- Diagnosed by high CK-MB
- May present with shock – myocardial dysfxn
- Rarely get CCF, gallop, hypotension, vasc collapse
- ECG: flat T waves, ST depression, abn Q waves (ant/inf infarction)
- CXR: varying degrees of cardiomegaly. In severe cases – venous congestion
- Managemnt:
  - Supportive – correct acidosis, hypolglyc, oxygen
  - If severe – ventilatory assistance, inotropes, vasodilators, diuretics
  - Thallium uptake scan – diffusely impaired (myocarditis → normal uptake)

Infant of diabetic mum

- Increased incidence of VSD, TGA, CoA
- 10-20% have hypertrophic CMO ± obstruction
- Incr risk PPHN
- 5-10% have gallop ±
- Systolic murmur LSB due to LVOTO
- CXR: cardiomegelly with venous obstruction
- ECG: prolong QT± RVH, LVH, CVH
- LVOTO → propranolol. No LVOTO → digoxin and lasix

Supraventricular tachycardia

- HR>200-300bpm,
- WPW responsible for 50% SVT in NN

- WPW → anomalous condution between atrium and vent, bypassing AV node, prone to paroxysmal SVT
- Diagnosis PR – lower limits of normal (normal in age <3yrs = 0.08), initial slurring of QRS (delta wave), wide QRS
- Other causes: Ebstein. TA. Cardiac tumours, thyrotoxicosis, viral myocarditis
- Drug of choice: adenosine, 50 microgram/kg at 1-2mins, increasing every 2 mins till reach 250 microgram/kg. If unresponsive and in CCF – cardiodivertion - then digitilise and lasix. If no CCF – digitalise alone
- May use vagal manoevures

Atrial flutter

- Cardioversion then digoxin

Myocarditis

- Poor heart tone, gallop, increased heart rate, tachypnoea
- Low QRS voltages
- Radionucloid scan – inflammatory and necrotic changes
- Diff diag → dil CMO/EFE
- Treatment: Bed rest, diuretics, inotropes. Cautious use of digoxin at half the normal dose. Captopril may be useful. May use gamma globulin 2g/kg over 24 hrs as an immunomodulating agent

Acyanotic

- Check BP - myocardial function
- LVOTO → Propranolol
- LV dilatation with decreased contractility → digoxin and diuretics

Significant PDA

- Stiff lungs ±
- Bounding pulses, continuous /systolic murmur – mid/upper LSB
- CXR: high CTR, pulm venous cong
- **ECG:** LVH in small and BVH in large PDA. If PVOD develops RVH
- CXR – increased pulm vascular markings, cardiomegaly of varying degrees
- If PVOD develops → normal heart size
- **Management**
- Spontaneous closure of congenital PDA – small chance
- Can lead to Pulm HT – hyperactive praecardium
- In preterms: Indometh 0.2mg/kg 12 hrly. Upto 3 doses if urea and Cr normal platelet > 80 000. No bleeding tendancy and no NEC, no hyperbilirubinaemia. If indometh contraindicated or term infant –Sx

HYPERTENSION

Types of Hypertension

Adult	Systolic	Diastolic	Children/adolescents
Normal	<120	<80	<90th percentile
Prehypertension	<140	>90	90th – 95th percentile
Stage 1 HTN	<160	<100	95th – 99th percentile
Stage 2 HTN	≥160	≥100	≥5mmHg + 99th percentile value
Hypertensive urgency	>180	>110	
Hypertensive emergency	>180	>110 + EOD	

Types of HTN in children (Parks p474)

1. Hypertension

- Systolic & diastolic PBs levels that are greater than 95th percentile for age, gender and height on least 3 occasions
- In adolescents and adults BP levels .120/80 mmHg are considered hypertensive even if they are less than 95th percentile

2. Pre hypertension

An average systolic & diastolic BP between 90th and 95th percentile for age gender and height

When BP > 95th HTN can further be classified as under

- <u>Stage 1 HTN</u>

  Stage 1 HTN is present when BP readings are between 95th – 99th centile

- <u>Stage 2 HTN</u>

  Stage 2 HTN is present when BP readings are 5 mmHg or more above the 99th percentile values

3. White coat HTN

White coat HTN is present when BP readings in health care facility are >95th centile but normotensive outside the clinical settings

Etiology of hypertension

Pneumonic – NERVO: Neurologic, Endocrine, Renal, Vascular, Others: Tumors, Drugs, Miscellaneous

A. Neurological

- Familial dysautonomia (Riley-Day syndrome)
- Increased ICP
- Bulbar polio
- Anxiety

B. Endocrine

- CAH
- Hyperaldosteronism
- Cushings syndrome
- Hyperthyroidism

C. Renal causes

- CRF and post renal transplant
- Renal parenchymal dx
  - Scaring due to reflux nephropathy / obstructive uropathy
  - Acute or chronic GN
  - Renal dysplasia
  - Polycystic kidneys
- Renovascular dx
  - Renal artery stenosis
  - Renal artery thrombosis
  - Renal artery aneurysm
  - A-V fistula
  - Vasculitis (polyarteritis nodosa)
- Renal tumours
  - Nephroblastoma
  - Hamartoma
  - Hemangiopericytoma

D. Vascular

- Coarctation of aorta
- Takayasu arteritis

E. Tumours

- Pheochromocytoma
- Wilms Tumor

- Neuroblastoma
- Ganglioneuroma
- JG cell tumour

F. Pharmacological

- Steroids
- OCP
- Catecholamines
- Amphetamines
- Reserpine
- Heavy metals – lead
- Licorice
- Salt excess
- Caffeine

G. Miscellanoeuos

- Essential HT
- Burns
- Prolonged immobilisation

<u>Some selected important causes of HTN are listed as under:</u>

Acronym: **P**inki **C**ares **H**er **H**usband **A**nd **P**uts **R**ed **C**olored **S**alt **N** **V**inigar **U**nder **H**is **A**rmpits **O**ne **T**ime

- P Pyelonephritis
- C Co-arctation
- H Hyperaldosteronism
- H Hyperthyroidism
- A Acute renal failure
- P Pheochromocytoma
- R Renal artery stenosis
- C Cyslosporin
- S Steroids
- N Neurofibromatosis
- V Vasculitides
- U Umbilical artery catheterisation
- H Haemolytic uremic syndrome
- A Adrenogenital syndrome
- O Obesity
- A Tachyasu

Markers of progressive organ damage

1. Serum creatinin
2. Urine output
3. ECG results
4. Haemodynamic monitoring
5. Finding on CXR
6. Pts neurological status
7. Findings on ocular examination
8. Cardiac echo – most reliable (LVH)

First sign of HTN in children is intraventricular septal hypertrophy so do Cardiac Echo in all HTN children. Then heaving, loud P2 and then retinopathy (Prof Bhimma 11.05.2011)

In adults → LVH

APPROACH TO THE EVALUATION OF A HYPERTENSIVE CHILD

- Usually children have secondary hypertension - 90% due to renal dx
- Normograms need to be used to plot child's BP in relation to age and body stature
- Establish HTN first and then look for signs of established complications
- Note if the HTN is peristant or transient

Clinical symptoms in infants

- CCF- 64%
- FTT and vomiting – 46%
- Respiratory distress – 25%
- Irritability – 18%
- Convulsions – 7%

Clinical symptoms of older children

- Headach
- Nausea, vomiting
- Encephalopathy
- Polydipsia/polyuria
- Visual problems – retinal damage due to damage to optic nerve
- Facial palsies LMN, damage to vasa varum

Clinical clues for secondary hypertension

- Fever, pains, dysuria **– Pyelonephritis**
- Leg pain on exercise; Turner's – **Coarctation**
- Polyuria, weakness, muscle cramps, constipation – **Hyperaldosteronism**
- Wt loss, sweating, fine tremor – **Hyperthyroidism**
- Anorexia, vomiting, dehydration, oedema, palpable kidneys, acidotic breathing, disturbed LOC **- Acute renal failure**
- Palpitations, sweating, flushing, pallor – **Pheochromocytoma**
- Trauma, bruits, abdominal tumor, renal transplant – **Renal artery stenosis**
- Drugs – **Cyclosporine, Steroids**
- Café au lait spots and lumps – **Neurofibromatosis**
- Joint pains, rash, fever, oedema, decreased pulses – **Vasculitides**
- Sick neonate – **Umbilical artery catherization**
- Bloody GE, oliguria, pallor, oedema, petechiae - **Haemolytic uremic syndrome**
- Secondary sexual disorders – **Adrenogenital syndrome**
- BMI > +2 SD, adiposity, acanthosis nigricans, hirsutism, hepatomegaly **– Obesity**
- Dimin/absent radial pulses, dil cardiomyop, malar rash, interst lung dx, ulcerative colitis, RA, polymyositis– **Takayasu**

CNS causes of raised ICP

- Transverse myelitis
- GBS
- Tuberous sclerosis
- Neurofibromatosis

Causes of acute hypertension

- Acute glomerulonephritis
- Henoch schonlein purpura
- HUS
- Acute renal failure
- Follwing ureteral surgery/transplantation
- Acute hypovolaemia

Causes of sustained hypertension

- Renal nephropathy
- Obstructive nephropathy
- Glomerular dx – 70% bilateral, 30% unilateral
- Tumours – Wilms, heamangioblastoma
- Gordons syndrome – increased proximal tubular reabsorption of sodium and chloride; pseudohyperaldosteronism type II; hypertension with decreased rennin and increased potassium. Treatment: Thiazide diuretics

Investigations (Parks p480)

Decision to undertake a special investigation depends upon:

- Avaibility of procedure
- Severity of HTN
- Age of patient
- History & physical findings

Example:

- Child <10 yrs with sustained HTN requires extensive investigations
- Adolescent with mild HTN & family hx of essential HTN does not req extensive investigations

FIRST LINE INVESTIGATIONS		
1	FBC, CRP	Septic markers, plt (HUS)
2	Urine analysis & mcs Urea, creatinin, uric acid	Renal parenchymal dx
3	Serum electrolytes (Hypokalaemia)	Hyeraldosteronism (primary/secondary) Adrenogeniotal syndrome Hyperfunction of adrenal gland Renin producing tumour
4	CXR, ECG, Cardiac echo	Cardiac cause of HTN, also base line function
SPECIAL INVESTIGATIONS		
5	Plasma renin activity	High renin HTN • Renovascular HTN • Renin producing tumors • Some Cushings syndrome • Some essential HTN Low renin HTN • Adrenogenital syndrome • Primary hyperaldosterone
6	24 hr urine collection for 17-ketosteroids 17-hydroxy corticosteroids	Cushings syndrome Adrenogenotal syndrome
7	24 hr urine collection for Catacholamine levels & VMA	Pheochromocytoma Neuroblastoma
8	Aldosterone	Hyperaldosteronism Renovascular HTN Renin producing tumors
9	Renal vein plasma activity	Unilateral renal parenchymal dx Renovascular HTN Tumors – Wilims, Neuroblastoma
10	Abdominal aortogram and selective renal angiography	Renovascular HTN Abdominal co-arctation of aorta Unilateral renal parenchymal dx Pheochromocytoma
11	Intra-arterial digital subtraction angiography	Renovascular dx
12	Technetium 99 DMSA	Renal parenchymal dx

Treatment

- Rational use of antihypertensive depends on severity, duration and cause
- Treatment modalities include medical, surgical or a combination of both
- Nephritic syndrome is characterized by hypervolaemia and requires diuretics
- In salt wasting conditions example CAH – get increased angiotensin II. Treatment – saline and mineralocorticoids
- BP should be lowered in controlled manor to avoid risk of hypoperfusion of vital organs which can cause ischaemia & infarction. BP be monitored every 5-10 min
- Reduce BP by 1/3 of what it is, then by 1/3 in the next 48hrs, then stabilize over the next 72hrs

Drugs used in management of hypertensive crisis

	Drug	Dose	Comments
1	Sodium nitroprusside	0.5 – 8 micrgram/kg/min ivi	Headach, muscle spasm, flushing
2	Labetalol	0.2-2 mg/kg/hr/ivi drip Acts in 205 minutes	bronchospasm
3	Diazoxide	3-5 mg/kg ivi bolus	
4	Hydralazine	0.15 mg/kg ivi or imi Dose may be repeated in 4-6 hrs interval	ivi onset 10 minutes imi onset 20-30 minutes
5	Nifedipine	0.25 - 0.5 mg/kg oral Every 4-6 hrs in sever cases	
6	Furosemide	1 mg/kg ivi to initiate diuresis	
7	Diazepam	0.2 mg/kg or another anticonvulsant for seizures	
8	Clavidipin	1-2 mg/hr (adult) onset 2-4 minutes Duratoion 5-15 min Contraindic: allergy to soya, & egg,	New FDA approved (2008) SE: Headach, NV, hypotension, rebound HTN, reflex tachycardia, increase in lipids

Management of sustained and moderate hypertension

- First line: Propranolol, hydralazine, prazosin, nifedipine
- Second line drugs: Minoxidil, clonidine, ACE inhibitors

Management of mild hypertension

- Salt restricted diet, wt reduction, potassium rich foods, regular aerobic exercise, no smoking/contraceptive pills
- Nifedipine, diuretics and beta blockers

Management of reno-vascular hypertension

- Surgical: Nephrectomoy – total/partial, concomittent antibiotic therapy for infectious process + general supportive measures
- Nephrectomy – if dx is unilateral
- Angioplasty or embolization

Cardiovascular disease

Surgical or catheter interventional correction for COA and other CVS causes of HTN

A POLULAR APPROACH

5th choice	Vasodilator: Hydralazine: 0.75mg/kg/d
4th choice	Ca Channel Blocker: Nifedipine: 0.25mg/kg/d Amlodipine: 2.5-5mg/d
3rd choice	ACE Inhibitor: captopril 0.3-0.5mg/kg/dose or ARB: Losarten: 0.7mg/kg/d
2nd choice	Beta Blocker: Propranolol: 1-2mg/kg/d or Atenolol: 0.5mg/kg/d
1st choice	Diuretic: Hydrochlorothiazide: 1mg/kg/d (6.25/12.5/25mg)

Contraindications to antihypertensive drugs

Asthma	Beta blockers
2nd or 3rd degree heart blocks	Beta blockers, Dihydropyridine Calcium CB
Chronic Obstructive Pulm Dx	Beta blockers
Gout	Thiazide diuretics
Heart failure	Non-dihydropyridine Calcium CB, Alpha blockers
Renal insufficiency	Potassium sparing agents
Depression	Beta blockers, central alpha agonists, Reserpine
Renal artery stenosis	ACE inhibitors

Hypertensive crises

Hypertensive emergency	Hypertensive urgency	Accelerated malignant HTN	Hypertensive encephalopathy
Immediate BP reduction in minutes→ use parenteral therap	Reduction of BP needed within hrs → use oral therapy	Situation in which papilloedema, haemorrhage & exudate are associated with marked BP increase. Diastolic is usually >140	Markdly raised BP is associated with sever headach & alteration of consciousness

Followup evaluation

1. Follow-up examination includes:
   a. Ongoing BP monitoring

b. Evaluation of target organ damage
c. U/E monitoring
d. Counseling regarding CVS risk factors
e. Adherance to newly adopted healthy lifestyle

2. Goal of treatment: reduction of BP
   a. $<95^{th}$ centile in uncomplicated HTN
   b. $<90^{th}$ centile in children with CRD, DM, hypertensive organ damage

3. Step down therapy
   In selected primary HTN patients

TACKAYASU ARTERITIS

Pulseless dx is a chronic vasculitis (chronic Giant cell arteritis) which segmentally affects large vessels particularly aorta and its major branches (Nelson p1094)

- It is the 3rd common form of childhood vasculitis after KS and HSP, predominently in females
- Exposure to TB has been associated with dx in Asia with positive Mantoux bot no other sigs of TB are usually present
- HTN is the most commonly present followed by CCF, bruits and absent pulses
- Absent of BT Shunt scar is an important negative finding in pulseless dx (Dr Mubaiwa)

Clinical manifestations:

- Night sweats, anorexia, wt loss and fatigue
- Myalgia nd arthritis
- Unexplained HTN
- Uveitis – may be a presenting complaint
- Interstitial lung dx – pneumonic consolidation
- Ulcerative colitis, rheumatic arthritis, polymyositis
- Dermatological features:erythema nodosum, malar rash, erythema induratum
- Cardiac: dilated cardiomyopathy, myocarditis, pericarditis

Diagnostic criteria (Coovadia p454)

Angiographic abnormalities of aorta or its main branches + one of the following featurs:

- Reduced peripheral artery pulses or claudication of extremities
- BP difference of >10mmHg
- Brui over aorta/main branch
- HTN (according to centiles)

Laboratory diagnosis (first simple non-invasive then diagnostic)

- FBC, raised IgG
- ESR>60
- Microcytic hypochromic anaemia with leukocytosis
- Polyclonal hypergammaglobulinaemia
- Angiography to confirm diagnosis
- MRI – non invasive for frequent monitoring of affected muscles

Traetment

- Aim at controlling HTN & seizures and signs of inflammation
- Early identification and surgical excision of predominant lesion
- Immunosuppressive therapy – prednisolone
- Methotrexate in some situations
- Cyclophosphamide to control intense inflammatory response
- Treat HTN & control seizures

RHEUMATOLOGY

ARTHRITIS AND LIMB PAIN

HISTORY
- Duration of arthritis
- Morning stiffness
- Progression of illness
- Family history of spondylitis, easy bruising, bleeding disorder or TB
- History of dysentery
- Easy bruising

EXAMINATION
1. General
- III: spiking temperature (systemic JCA)
- Lymphadenopathy – diffuse
- Pallor
- Gingival hypertrophy
- Sternal tenderness
- Mantoux and BCG
- Look for side effects of medication e.g., steroids, aspirins, NSAIDs

2. Skin
- Rashes – of JIA, SLE, Rheumatic fever, erythema chronicum migrans, Lyme dx, mixed connective tissue disorder (MCTD), viral exanthemas, subcutaneous nodules
- Psoriasis
- Skin infections due to immune deficiency esp IgA
- Atrophy of skin and skin texture – thickening from scleroderma or sclerodactyly

3. Eye
- Conjunctivitis, iridocylitis (irregular pupil), uveitus, dry eyes, cataracts (steroid induced)

4. Face:
- Parotitis, macroglossia or dry mouth

5. CVS
- PFR, murmurs, tachycardia (carditis – mitral or aortic regurgation)

6. Chest
- Decreased movements due to pain at c-c joints and sterno clavicular joints, stridor due to affectation of crico-arytenoid joint

7. Abdomen
- Hepatosplenomegaly may be found (activation of RE system – systemic onset like JRA, SLE)

8. Musculoskeletal
- Test all joints
- Do not forget cervical, TM, spine and sacro-iliac
- Note no. of joints involved and whether they are big/small and symmetrical/asymm
- Look for swelling and thickness incl synovial thickening (pannus), limited movement of muscles esp small ms of hand
- EIllicit fluid in joints – patellar tap
- Contractures, joint deformities and deviations

9. Urine
- Proteinuria due to secondary amyloidoisis
- Heamaturia due to drugs e.g aspirin

DIFFERENTIAL DIAGNOSIS OF JOINT PAINS

1. **Infections:** Septic arthritis/osteomyletis, viral (rubella, EBV, parvo, Lyme dx)
2. **Malignancy:** Leukemia, neuroblastoma, primary tumors of bone and cartilage
3. **Connective tx dx:** SLE, dermatomyositis, scleroderma, MCTD
4. **Vasculitis**: HSP, Kawasaki
5. **Reactive arthritis:** Post dysentery (shigella, salmonella, yersinia), post strep, meningococcal or Haemoph Infl meningitis
6. **Heamatological d/o**: Sickle cell, thalassemia, heamophilia
7. **Orthorpaedic d/o:** Perthes, slipped femoral epiphysis, chondromalacia patella
8. **Miscellaneous:** Gout- primary/secondary, hypermobility (p/s), sarcoidosis, familial medit, fever
9. **Psychogenic**

EXCLUDE ALL THE ABOVE DS BEFORE DIAGNOSING JCA

Examination of patient with joint swelling – (tutorial in B1E)

Salient points noted in tutorial

Opening statement: patient with multisystem disease & involvement of joints
- Which joints are involved in which disease?
- If SLE susp – ask for urine dipstix (immune complexes would deposit in kidneys)
- If joints still painful → active disease
- Joint swelling, effusion, tenderness
- Erythema from increased blood flow
- Joint contractures
- Joint lining – or synovium may be thickened from chronic inflammation
- Oedema of the eyes may be due to allergy
- Nails – pitting – psoriasis, SLE, TS (Trisi)

- Look for bursitis & feel for calcifications
- Always examine cervical and TM joints
- Stiffness if these are worse in the morning
- Limb length discrepancy – due to activation of epiphyseal growth plates in an area of arthritis can lead to localized bony proliferation and LL discrepancy
- Maldevelopment of bones: inflammation at thr site of immature growth centres may lead to maldevelopment of bones (overcrowding of carpals & tarsals) or temporomaandibular joints → micrognathia
- Abdominal pain – vasculitis of visceral peritonitis
- Especially look for effusions and pleuritis
- Restriction of chest movement: do lung function tests (immune complexes → interstitial pneumonias, reduced lung expansion → restrictive lung disease
- Genetic markers
- Treatment: pain management, anti-inflammatory, steroids, disease modifying agents

Henoch-Schonlein Purpura – (Mock FCP presented in B1E also see Coovadia p453

Opening statement: 9 yrs old little boy with rheumatological disorder
Achronyme: SANDS – TEES - SYSTEMS

Scene: patient with iv line on PMS, dressing on the right renal area and urine container lying on the bedside: → possibly post renal biopsy
Anthropometry: draw triangle of nutritional assessment: normal
Neurodevelopmetal assessment: appropriate for his age
Dysmorphism: nil
Tanner stage: prepuberty
Eyes: no keratitis, uveitis, conjunctivitis
ENT: no tonsillitis / adenoids
Skin: non-blanching palpable purpuric rash –on lower limbs & buttocks preferably, no heliotrope (JDM), or butterfly (SLE) rash noted
GPE: pale, no wet petechiae, normal temperature
GIT: diffuse abd tenderness but no signs of acute abdomen (intussuception or intestinal obstruction)
MSK: swelling and pain of 3 MCP joints right hand (1^{st}, 2^{nd}, 3^{rd}), no limb length discrepancy
Respiratory: no features of interstitial pneumonia, no signs of pleural effusion or pleuriris
Renal: urine dipsticks → proteinuria^{+2}, haematuria $^{+2}$
CVS & CNS: normal

Assessment:
9 years old male child with possible rheumatological disease which is most likely Henoch-Schonlein purpura as evidenced by the tetrad of symptoms:
1. Palpable purpura
2. Diffuse abdominal pain

3. Arthritis / arthralgia
4. Renal involvement (proteinuria & haematuria)
5. Possibly renal biopsy has been taken to look for deposition of IgA deposition

Differential Diagnosis

- ITP
- Drug reaction – no drug history
- SLE – no mallor rash
- JDM
- Meningococcaemia – no signs of meningitis
- Leukaemia – no LAD or HSM
- Urticaria – no periorbital swelling / rash not itching

Investigations:

Bedside: Urine dipstix, stool observation for blood in stool
Laboratory: FBC (normal platelets and to exdclude other causes), Serum IgA (70% children do have it raised but normal does not exclude HSP

Management:

Non-complicated HSP

- No treatment
- No steroids
- Counsel parents about relapse rate in 1/3rd of cases

Complicated HSP

- GIT symptoms – put on proton pump inhibitors
- Artheritis – oral steroids (1-2 mg/kg/day) for 2weeks
- Non-steroidal anti-inflammatory drugs: oral steroids reduce progression of renal dx. If already has dx – pulsed methylprednisone especially if crescents observed on biopsy. If does not help – cyclophosphamide, azathioprine
- Polygam – ivi immunoglobulines

Exam questions:

What is the etiology of HSP?

- Immune mediated (skin cells, glomerular cells)
- Post infectious – post streptococcal
- Post vaccination
- H_1N_1

What are complications of HSP?

- GIT: ac abdomen, raised amylase, vasculitis of stomach, intussception – malena stools
- Eyes: uveitis
- Arthroitis: 1-4 joints involvement
- Renal: nephrotic syndrome / haematuria / proteinuria
- Relapses are associoated with URTI – and are prevented by prophylactive penicillin

ENDOCRINOLOGY

Approach to a child with obesity

(Diabetes mellitus and practical endocrinology p173)

Opening statement: obese child
Acronym: SAND-TEES-SYSTEMS
Scene:
Anthropometry:

- BMI
- Subcutaneous skin fold thickness
- Waist circumference
- Rapid growth & physical dev, tall stature, increased ht velocity →simple obesity
- Short obese , growing slow → endocrine abnormality
- Associated dysmorphism + MR → syndromic cause

Neurodevelopmental assessment

- Hx of large for gestational age
- Psychological problems
- Vitims of redicule – more passive inactive style

Dysmorphism: look for features of the following syndromes:

- Laurence-Moon Biedl
- Pseudohypoparathyroidism
- Prader-Willi
- Beckwith Wiedemann
- Klinfelter's

Tanner: look for signs of precocious puberty
Eyes:

- Retinitis pigmentosa, looks syndromic & MR → LMB
- Impaired visual feildes, papilloedema or optic atrophy → intracranial tumor / crangiopharyngioma
- Heart failure, vision problems, dev delay, learning disabilities, sensory hearing loss, DM→ Alstrom-Hallgren syndrome

ENT: snoring, night time coughing, obstructive sleep apnoea

Skin: acanthosis nigrican (NIDDM), purple skin stria & buffalo hump (Cushings)

GPE: look for goiter

Abdomen: truncal obesity → hypothyroidism / Cushings syndrome)

Marked suprapubic fat pad → penis being buried in fat → small penis → impared self image → inadequate development of secondary sex chracters → hypogonadism

Chest: impaired cardiorespiratory function

- Hypoventilation alone → **Pickwickian syndrome** (obesity hypoventilation syndrome leading to hypoxia and hypercarbia resulting in obstructive sleep apnoea)
- Tonsillary hyperventilation & airway obstruction → **Chubby Puffer syndrome** (UAO and obesity, with intermittent somnolence & cardiorespiratory embarrassment)

CNS:

- Hypotonia, MR, hypogonadism, short stature → Prader Willi
- Dry itchy skin, poor muscle tone, bradycardia, easy fatigue → Hypothyroidism
- Moon face, hyperhidrosis, stria, proximal myopathy → Cushings syndrome
- Growth retardation, retarted dev of genital organs → Frohlich's syndrome

Musculoskeletal:

- Tall stature, increased height velocity → simple obesity
- Short stature & decreased height velocity → endocrine problem (GH def, hypothyroidism, Lawrence-MB, Prader willi, pseudohypothyroidism)

Investigations:

- X-Rays – advanced bone age → pseudohypothyroidism
- GTT, lipid profile, TFTs, LFTs, 24 hrs urinary cortisol estimation, LH, FSH, Oestradiol, 17-OH progesterone & testosterone
- Pelvic ultrasound → polycystic ovaries

SHORT STATURE

Definition
In a population 2SD below mean for height. Twenty percent will have pathological short stature and 80% familial short stature and constitutional growth delay. Children 3SD below mean for height must have pathological short stature. Three percent of normal children arwe 2SD below mean for height

Growth determinants
Nutrition, genetic, environment (emotional deprivation), and hormones (cortisol, sex hormones, thyroid hormones and insulin)

When to investigate?
- Short with obesity
- Short with dysmorphism
- Female with shortness example Turners
- Short with metabolic problems

General principles
- Growth best evaluated in terms of velocity/growth rate
- In infants selected measurements are wt, ht and OFC
- In older children and adolescents – ht and wt

Osseous development
- Based on time when ossification centres appear and epiphyseal and diaphyseal union occurs
- In the newborn X rays of knee/ankle/foot are informative
- In infancy, childhood and adolescents X rays of wrist, hand, and left elbow are essential
- Retarded osseues development occurs in hypopituitarism, hypothyroidism, malnutrition, constitutional dwarfism, chronic dx states, severe illness, male hypogonadism and delayed adolescence.
- Accelerated development occurs in sexual precocity and patients with obesity

Growth patterns
- Short stature: Length/height 3 SD below mean for age or when velocity of growth below that expected for chronological age
- Best to use Ht velocity curves when Ht increment in cm/yr is plotted against chronological age
- Growth in Ht is finally terminated by epiphyseal closure
  - A rate of < 5cm/yr during the period of 5 yrs to the onset of adolescent growth spurt is subnormal.
  - A growth rate <6cm/yr between the age of 2-5 yrs is subnormal
- In males, the peak Ht velocity occurs at the age of 14 & during Tanners stage 4 where as in females it peaks at the age of 12 and Tanners stage 2 after breast budding and a year before menarche

- Hereditary factor is a main determinant of the pattern of linear growth

Skeletal proportions

A). Measure the child's height

- Measure the lower segment (LS) → pubic symphysis to ground
- Calculate the upper segment (US) → by subtracting the LS from the total height
- Calculate US/LS ratio

  Normal values
  - at birth 1.7
  - 3 yrs 1.3
  - 8 yrs 1
  - 18 yrs 0.9

If:		
US/LS ratio ↑	Short lower limbs	skeletal dysplasia, hypothyroidism
US/LS ratio ↓	Short trunk	vertebral radiation, scoliosis
	Short neck	Klipple-Feil sequence

B). Measure arm span (AS) & minus from it the total height (H)

- **Calculate AS–H**

  Normal values
  - From birth to 7 yrs - 3 cm
  - From 8-12 yrs 0 cm
  - At 14 yrs
    - Boys +4 cm
    - Girls +1 cm

If:			
AS – H = < N	and US/LS ↑		Short limbs / normal trunk
AS – H = > N	and US/LS ↓		Normal limbs / short trunk
AS – H = < N	and US/LS ↓	or N	Short arms / short trunk

CLASSIFICATION OF SHORT STATURE

Introduction

- 80% normal with familial stature/constitutional delay, 20% pathological
- Of those that are pathological they either be proportionate or disproportionate
- **Proportionate short stature** may be due to prenatal or postnatal causes:
  - Prenatal causes are IUGR (placental insufficiency, infections, teratogens), dymorphic syndromes and chromosomal disorders e.g., Turners
  - Postnatal causes are of endocrine origin (Cushings, hypogonadism, pshychosocial dwarfism), malnutrition, GI dx, cardiopulmonary dx, chronic aneamia, renal disorders, drugs esp steroids
- **Disproportionate:** Short stature may be due to skeletal dysplasia example achondroplasia, rickets

Classification of Short Stature:

- Familial (genetic) short stature
- Constitutional growth delay
- Short stature following IUGR
  - Proportionate
  - Disproportionate)
- Skeletal dysplasias
- Endocrine disorders
- Chronic diseases
- Psychological deprivation
- Dysmorphic syndromes

SHORT NOTES

FAMILIAL SHORT STATURE

- Small at birth but grow parallel to normal curve though below 3rd centile
- Achieve small adult height – males<163cm and females <150cm
- No lab or clinical evidence of endocrine/systemic dx
- Annual growth rates within normal limits
- Bone age appropriate for chronological age
- No treatment
- Exercise caution in making diagnosis of familial SS

CONSTITUTIONAL DELAY

- Constitutional means part of child's make-up
- Combination of slow growth and lack of meaningful virilization
- Slow physical maturity is the hallmark
- Grow for longer period to attain adult height
- Normal at birth – shortness after 6 months age and then by 2 yrs - ht <5th centile
- Positive family history of delayed puberty

- Treatment: (controversial). No evidence that final ht is increased by hormonal treatment. **Conventional treatment**: Low dose testosterone monthly for 6 months, synthetic steroids accelerate growth

INTRAUTERINE GROWTH RETARDATION

- It may be symetrical or asymmetrical
- Symmetrical: Foetal growth retardation consists of a reduction in wt, length & OFC related to early growth failure
- Asymmetrical: GF with preservation of head growth occurs because of late deprivation of nutrients like placental insufficiency. Potential for post natal growth catch-up is less in symmetrical compared to asymmetrical
- Small for gestational age is defined as birth weight less then 10^{th} centile for gestation (some books state less than 3^{rd} centile).
- IUGR is isolated finding but may also be associated with multiple congenital malformations, usually sporadic
- No family history
- Normal growth and endocrine studies
- Possible causes: Twin pregnancy, maternal nutrition, PIH and IUI, maternal smoking and alcohol abuse
- Diagnosis depends on length of gestation and weight and length at birth
- Children may show catch up growth though some fail to do so
- Catch-up growth is reduced in fetus with symmetrical growth retardation, 85% will show catch-up growth by 5 yrs of age

SKELETAL DYSPLACIA (Endocrine p56)

- Osteochondrodysplasias → primary bone and cartilage disorders
- Characterized by disproportionate short stature with abnormalities in size and shape of limbs, skull, spine and pelvis
- Careful measurements of sitting ht, arm span, US/LS and skeletal survey is needed for diagnosis
- In classical disorders e.g., achondroplasia (severe limb shortening with characteristic skull and facial abnormalities) skeletal survey not required
- Always exclude hypothyroidism when appearance of multiple epiphyseal dysgenesis on X ray

ENDOCRINE DISORDERS

- Growth hormone insufficiency: Immature appearance: excess subcutaneous fat, micropenis, hypoglycaemia
- Hypothyroidism: untreated congenital/acquired/autoimmune thyroiditis
- Cushings syndrome: height <3^{rd} centile in 505 cases
- GH resistance: Laron syndrome – mutation of GH receptor. Prominent forhead, blue sclera, delayed dentition & bone maturation, reduced blood glucose (B Nelson p759)

CHRONIC SYSTEMIC DISORDERS

Chronic dx of any system may interfere with growth

- **Nutritional unsufficiency** is most common cause, characterized by loss of subcutaneous tissue, muscle wasting and with elevated GH and low insulin-like growth factor levels
- **Chronic GIT dx** e.g Coeliac/Crohns
  - **Coeliac dx:** Apathy, anorexia, recurrent GE, abdominal distension, diagnosis by careful history regarding quantity and quality of stools. May need jejunal bx. Coeliac panal: antibodies to tissue transglutaminase. Pt has blunted GH response to provocative stimuli or GH may be normal with low IGF levels. Treat with gluten free diet
  - **Crohns dx:** Growth failure present before abdominal and bowel complaints. Children show low energy intake with negative nitrogen and energy balances. Diagnosis by endoscopy and radiological studies
- **Chronic kidney dx:** CRF, RTA, Barter's – minimal signs and symptoms. Diagnosis with biochemical studies. Growth failure likely when GFR fall<25 ml/min/1.73m^2. Growth failure may be associated with renal osteodystrophy (hypocalcaemia, hyper phosphateamia, metabolic acidosis and compensatory increases in PTH)
- **Cardiac dx**

PSYCHOLOGICAL DEPRIVATION

- Type I: children <3yrs → non organic FTT
- Type II: older children with SS and GH insuff
- Hyperphagic short stature: abnormal behaviour with hyperphagia, polydipsia & growth failure
- GH insuff and resistance to exogenous GH therapy
- Sequential heigths and weights may provide the only quantitive evidence of neglect

DYSMORPHIC SYNDROMES (Endocrinolody p50)

1. **RUSSELL SILVER SYNDROME**
   - X-linked dominant
   - Low weight for gestational age – prenatal or IUGR
   - Diminished subcutaneous fat
   - Triangular face, prominent forehead, small mandible
   - Clinodactyly of 5th fingers
   - Post natal growth deficiency → short stature
   - Increased risk of learning disabilities
   - Hemihypotrophy
   - Presence of café-a lait spots
   - Potential role for GH

2. **TURNER SYNDROME**
   - 50% have 45X other 50% mosaicism and structural abnormalities of chromososme X or Y
   - Clinical features: low hair line, web neck, cubitus valgus, wide spaced nipples, short legs, short 4^{th} & 5^{th} metacarples, lymphedema, co-arctation of aorta, gonadal dysgenesis (gonads are streaks of fibrous tissue), renal abnormalities (horse shoe kidney), cutaneous navi and increased carrying angle
   - TS cannot be diagnosed or excluded clinically

3. **NOONAN SYNDROME**
   - Characteristic facies - ptosis, hypertelorism, low set ears
   - Low hair line, web neck, pectus carinatum, cubitus valgua, cryptorchidism & pulmonary stenosis

4. **WILLIAMS SYNDROME**
   - 7q11.22 deletion

   Pneumonic WILLIAMS
   - W: Weight low
   - I: Increased calcium, stellate iris (radiating – arranged like a star)
   - L: Large mouth
   - L: Long filtrum
   - A: Aortic stenosis
   - M: Mental retardation
   - S: Swelling around eyes (periorbital puffiness)

5. **ARSKOG SYNDROME**
   - X-linked dominant
   - Hypertelorism, short nose, interdigital webbing, short broad hands, brachydactyle, shawl scrotum

Other syndromes like Prader Willi, Laurance MB, pseudohyporarathyroidism (are discussed elsewhere or see B Nelson p792)

FAILURE TO THRIVE

Organic causes

1. Gastrointestinal
   - Upper GIT
   - Oral malformations
   - Gastro-oesophageal reflux
   - Pyloric stenosis

2. Lower GIT
   - Cystic fibrosis
   - Coelic dx
   - Granulomatous enteritis

3. Congenital heart dx
   - Cyanotic CHD (TOF etc)
   - Acynotic CHD (PDA etc)
   - TORCH related (IUG failure)

4. Endocrine
   - Congenital hypopituitarism – growth failure, hypoglycaemia, diabeted inspidus, polyuria, polydipsia
   - Hyperthyroidism – poor feeding, loose stools, hyperactivity, tachycardia, tachypnoea, goiter, exophthalmos
   - Hypothyroidism –
   - Chronic adrenal insufficiency
     - Adrenal haemorrhage
     - Calcification
     - CAH
     - Addison's dx
     - TB of adrenals

5. Renal disorders
   - Obstructive renal dx
   - Glomerular
   - Nephrogenic diabetes inspidus
   - UTI – recurrent
   - RTA
   - Uretrovesical reflux

Other organic causes
- Neurological disorders (MR, CP)
- Muscle dx

- Chromosomal
- Recurrent chest infections
- Metabolic disorders
- Drugs (retalin, steroids)
- CLD, Asthma
- Rickets
- Congenital syndromes
- TB – or other chronic infections

Non organic causes

- Common during the first 2 years of life
- Emotional deprivation
- Psychological stresses
- Young mothers, large families, poor socioeconomic conditions
- Clinical features:
- Bizarre behavious
- Voracious appetite
- Extreme short stature
- Protuberant abdomen

Investigations

Primary

- Urine mcs, pH, SG, reducing subs
- FBC, Retics with diff, U/E, ESR, blood gas
- Stool if loose – reducing subs / for parasites
- Skin: mantous, CXR, GW/sputum, HIV testing

Admit and do secondary investigations

- Stool fat (72hrs)
- Sweat test
- Bone age
- Upper & lower GIT contrast study
- LFTs
- Serum proteins & IgG levels
- TFTs
- Small bowel biopsy

AN APPROACH TO A CHILD WITH SHORT STATURE

Physical examination:
Acronym: SAND TEES SYSTEMS

Scene:
Anthropometry and measurements:

- Draw triangle of nutritional assessment and assess nutritional status
- Weight
- Height
- OFC
- Additional parameters:
  - Upper segment
  - Lower segment
  - Arm span
  - Height velocity
  - Request parents' height
  - Onset of puberty

Neurodevelopment:
Dysmorphism: pt stands you sit and observe in detail about dysmorphism, disproportion

Tanner stage: note pubertal staging using criteria for Tanner & Prader orchidometer
Eyes:
ENT:
Skin:
GPE: Ask patient to do the following manouvers:

- Straight arms with palms together + legs together →look for asymmetry (RSS)
- Hold arms out straight with plams forward → access carrying angle → increase in Turners
- Touch tipe of thumbs to tips of shouldres:
- If thumbs overshoot – proximal limb shortening – Rhizomelia 9achondroplasia, hypochondroplasia)
- If thumbs do not reach shoulkders ther is middle segment limb shortening (mesomelia), or distal segment limb shortening (acromelia)
- Ask child to hold palms up – look for simian crease (Downs), clonodactyly (RSS)
- Make a fist – short 4^{th} metacarpal → pseudohypoparathyroidism
- Examine back – touch toes – look for scoliosis, kyphosis

Examine all systems: Respiratory, CNS, CVS, and GIT

Assessment: on the basis of your findings

Then request history and results of the followings;

- History of parental heights, birth weight, gestational age, mechanisms of delivery, development in infancy, pattern of growth, nutritional/social history and drug history
- Results of urine test – DM, CRF
- Stool analysis – malabsorption syndrome
- Sumamrise your findings and give succinct diagnosis then mention the following investigations:

Investigations: (Baby Nelson p795)

- Investigations depend upon clinical findings like height velocity
- And if the short stature is pathological or constitutional

Baseline investigations;

- FBC, ESR → chronic dx, anaemia (nutritional or malignancy)
- WCC → infection / inflammatory, leukopenia → bonemarrow syndrome
- U/E, Creatinin → chronic renal dx, adrenal dysfunction, acid base status
- CPM, LFTs→ Rickets, hypophosphataemia, chronic hepatitis

Special investigations:

- TFTs (T4, TSH) → hypothyroidism, hypogonadism
- Ferritin, endomyseal antibodies, tissue transglutaminase antibodies → coelic dx
- Cartisole, prolactin → elevatyed in hypothalamic dysfunction and reduced in pituitary dx
- Chromosome studies / Karyotype: if > 3 dysmorphic features or mental retardation and dysmorphism. Like in girls → Turners, Downs
- Skeletal survey in dysmorphic children → skeletal dysplasia
- Folate levels to reflect nutrition and rule out malabsorption
- Bone age, X ray → assess skeletal maturity – not a diagnostic test
    - Two methods: Greulick & Pyle (atlas method) &
    - Tanner-Whitehouse (bone specific scoring system)
- Urine analysis: renal function testing, urine pH & serum bicarbonate – to ascertain RTA
- MRI – hypothalamic pituitary tumors
- IGF1 or IGF BP3 – reflects GH status or nutrition
- **Bone age**: Left wrist and hand – use Greulich and Pyle method or TW2 method
- **Lab tests**: FBC, UE, ESR, urinalaysis, serum antigliadin titre, T4, T3 TSH. Calcium, alk phos, LFT, Sweat chloride test. Chromosome. Buccal smear test → inadequate
- Growth hormone alone – not useful
- Provocative tests
    - L-dopa and propranolol - S/E → vomiting, asthma attack
    - Clonidine – S/E → hypotension and sedation
    - Insulin – gold std - S/E → hypoglycaemia and seizures
    - GnRH, LnRH, TRH – S/E → facial flushing
    - Arginine infusion

  - Glucagon tests
- **Other tests**: Skull x-ray, CT scan and MRI – esp for hypopituitarism
  - Causes of low somatomedin levels
  - Probable GH def
  - Undernutrition
  - Acute illness
  - Hypothyroidism
  - Celiac dx/Crohns dx
  - Hepatic failure
  - Uncontrolled DM

DISORDER OF SEXUAL DIFFERENTIATION

- New term is complex genital anomaly
- Take detailed family hx
  - Parental exposure to exogenous/endogenous androgens, potential endocrine disruptors
  - Maternal virilization (increased body hair) during pregnancy
  - Consanguineous family (5 alpha reductase deficiency)

Classification of DSD

1. Overvirilizattion of female fetus (46XX DSD): AR. Leads to deficiency in enzyme function in the cortisol and aldosterone pathways. Most common 21 OH deficiency. ***Girls:*** present with ambiguous genetals, low Na, high K, eventually become dehydrated. ***Boys:*** present with dehydration and hyperkalaemia. Normal genitals therefore no clue to diagnosis
2. Undervirilization of male fetus (46XY DSD): defect in testosterone production or metabolism or action
3. True hermaphrodite (or ovotesticular DSD): ovotesticular disorder of sexual differentiation. Common in Central and Southern Africa. Both ovarian and testicular tissues are present. Diagnosis is confirmed on biopsy of gonads. Outcome regarding disability has been disappointing
4. Gonadal dysgenesis(45X/46XY mosaic): spectrum of disorders that lead to maldevelopment of the gonads and subsequently varying degrees of sexual differentiation

Stimuli that increase aldosteron secretion

- Cortisol secretion also increases
  - Surergy
  - Anxiety
  - Physical trauma
  - Haemorrhage
- Cortisol secretion unaffected
  - Increased potassium intake
  - Reduced sodium intake
  - Constriction of IVC
  - Prolonged standing

Regulation of aldosterone secretion (Ganong p379)
Increased ECF volume → increased renal arterial mean pressure → decreased discharge of renal nerves → inhibitory effect on juxtaglomerular apparatus → inhibited renin secretion → decreased production of renin angiotension II → inhibitory effect on adrenal cortex → reduced production of aldosterone → decreased sodium (and water) excretion → increased ECF volume

AN APPROACH TO DISORDER OF SEXUAL DIFFERENTIATION

Salient points to note when deeling with the newborn with DSD

- Both parents be seen ASAP
- Initial counseling by attending staff and senior paediatrician
- Key phrase: the way baby's genitals have been formed – we are not sure at present wether the baby should be brought up as a boy or girl
- Refer baby as the baby and not he, she, it
- Keep mom and baby in the single room
- Registration must be postponed
- Urgent investigations should be done withion 2 weeks for definite gender assignment

General examination (W Harris p108)

Skin for hyperpigmentation

Dysmorphism: features of Dany Drash, WAGR

Hydration – dehydration secondary to vomiting – CAH

Blood pressure – high in CAH – due to 11 beta-hydroxylase deficiency

Abdomen/ pelvis/genitalia

Abdomen: look for associated adrenal tumour

Inspect for Prader grading of virilisation of external genitalia:

Prader 0:	normal female
Prader 1:	enlargement of phallus (look more like clitoris; abnormal exposure to androgens beyond 8 week's gestation
Prader 2:	enlargement of phallus, vagina and urethra openings separate
Prader 3:	enlargement of phallus, urogenital sinus (single opening)
Prader 4:	enlarged phallus with hypospadias
Prader 5:	normal male

Inspect scrotum

- Fused, absent gonads – exclude XX with CAH
- Bifid, bilateral gonads present – undervirilized XY, true hermaphrodite with bilateral ovotestes
- Bifid, maldeveloped, bilateral gonads placed high – undervirilized XY, true hermaphrodite with ovotestes, dysplastic testes

Examine midline cleft / urogenital sinus

- Gently open cleft/sinus & confirm impression of Prader stage. Skin tags with purplish ting imply hymen is present
- If labioscrotal folds are partially fused/poorly formed asymmetrical possible ovotesticular -urogenital sinus

Palpation of gonads

- Gonads palpable bilaterally – can be brought to the base of the testes – <u>definitely male</u>

- Gonads palpable bilaterally - but placed high – undervirilized XY, true hermaphrodite, dysplastic testes
- Gonads palpable bilaterally but asymmetrical position - true hermaphrodite with testes on one side and ovotestes on other side
- Single gonad palpable – almost certainly testes – other may be ovary, streaked gonad or ovotestes - mixed gonadal dysgenesis
- Gonads impalpable bilaterally – cannot predict gonadal status
- Rectal examination should be mentioned – little finger can palpate a cervix and confirm a uterus
- Anal examination
- Measure phallus: normal size >2.5 cm at birth
- Note urine stream
- Note suprapubic fat

Meticulous description with diagram of abnormal genitalia

- Labio-scrotal folds
- Clinophallus
- Nature and size of opening below clinophallus
- Identification of urethral opening, vaginal opening, presence of and site of gonads
- Medical photography

INVESTIGATIONS

Diagnostic:

1. Genotype:
    i. Conventional karyotyping – may take 3 days
    ii. FISH to determine presence of Y chromosome
    iii. Buccal smear for barr body
2. 17 Hydroxy progesterone
3. Cortisol (11 beta hydroxylase, 21 hydroxylase, 3 beta HSD)
4. ACTH
5. Testosterone (17 beta HSD, 3 beta HSD)
6. Dihydrotestosterone (5 alpha reductase)
7. Dehydroepiandrosterone (17, 20 lyase)
8. Androstenidione (17, 20 lyase, 3 beta HSD)
9. HCG Stim test for testosterone or dihydrotestosterone
10. Pelvic US to define structures (uterus, intraabdominal gonads)
11. Androgen receptor gene mutation analysis
12. Urine collection for steroid analysis to exclude enzyme defects
13. Laparoscopy
14. Genitography to define vagina, urethra, bladder
15. MRI pelvis
16. Gonadal biopsy
17. Hormone profile at 2 ages: first 2 weeks, second 3 months

Complications:

U/E & plasma renin activity

RICKETS

Metabolic bone dx characterised by failure or delay in mineralization at epiphyseal growth plate due to abnormality in calcium, phosphate & vitamin D metabolism which leads to chronic bone deformaity.

Approach:

Rickets → stunting, approach as short stature

Renal osteodystrophy

Skeletal dysplasia → do US/LS ratios, symmetry of arms

- Osteogenic imperfacta
- Achondroplasia

Tutorial (combined haematology and renal – B1E, 28.09.2011)

Salient points of note:

- If tone normal → hypophosphatemic rickets
- If tone decreased → vitamin D deficiency
- Chovestic sign: tap in front of pinna just below zygomatic arch
- Drug hx: anticonvulsants
- X-rays with HPR – X-linked have subtle abnormalities not classical like vitamin D def
- Syndromes to exclude:
    - Wilsons dx
    - Cystinosis – blond hair, FTT, RTA (proximal)
    - Fanconi syndrome
    - Lowe syndrome
- **Treatment**
- 1 alpha calcidol
    - <20kg: 0.05mcg/kg start, can increase to 0.1mcg/kg/day
    - >20 kg: 1 mcg/od
- Calcium and phosphate
- GH not indicated
- Corrective surgery
- Osteotomy and rods – after growth plate is fused

AN APPROACH TO A PATIENT WITH RICKETS

Opening statement: metabolic bone disease

Scene:

Anthropometry: short statute, stunted

Neurodevelopmnemntal assessment: poor growth, learning difficulties with emotional liability

Dysmorphysm:

- Reduced IQ, short neck, round facies, short 4th metacarpals (MCs) & metatarsals (MTs) → pseudohypoparathyroidism
- Broad prominent forehead, short turned up nose with flat nasal bridge, overhanging upper lip → Willium's syndrome
- Bossing → vitamin D def

Tanner staging:

Eyes: blue sclera, cysteine crystals

ENT:

- Candidiasis, dental enemal, nail dystrophy → auto-immune hypothyroidism
- Delated dental eruption, & enamel hypoplasia, abnormal dentition → vitamin D def
- Deafness → OI
- Spontaneous abscesses → pseudohypoparathyroidism

Skin: alopecia, vitiligo, signs of Addison dx or hypothyroidism

GPE/JACCOLST: nail dystrophy, chvostek sign, trousseau sign (B Nelson p812)

SYSTEMS

Musculoskeletal

Swollen wrists, prominent costochondral junctions (rickitic rosary) & Harrison sulcus, bow legs and knock knees, craniotabes, muscle weakness – tetany, hyperextensable joints, scoliosis, kyphosis, genu varum/valgum, pigeon chest, wind swept legs → vit D def

CNS:

- Bossing / macrocephaly
- Hypotonia → Lowe syndrome, hypocalcaemia

Chest: pigeon chest, Harrison sulcus

CVS: peripheral stenosis

Abdomen: large protuberant abdomen/ hepa/ spleen → Tyrosenaemia, Galactosaemia

Differential diagnosis

- Hyperthyroidism
    - Autoimmune
    - Pseudohypoparathyroidism
- Vitamin D deficient rickets (nutrition, reduced absorption, increased metabolism)
- Vitamin D dependent rickets
    - Type I → alpha 1 hydroxylase deficiency
    - Type II → resistant to 1,25 DHCC
- Osteogenic imperfacta
- William's syndrome
- Fanconi's syndrome (cystinosis, Wilsons dx, tyrosinaemia, Lowe's syndrome)
- Heriditary hypophosphataemic rickets with hypercalciurea
- Renal tubular acidosis
- Renal osteodystrophy
- Prematurity (exclusive BF, soya milk)
- Neurofibromatosis with hypophosphataemia

Investigations

- X-rays wrists and long bones to confirm rickets (Essentials of Paed David Hull p242)
- Features of X-rays are as follows:
    - Cupping, splaying and fraying of metaphysis
    - Widening of epiphyseal plate
    - Thining of cartices
    - Periosteal reaction
    - Cystic lesions → hypophosphataemia
- U/E and bicarbonate: RTA. If no acidosis no need to do RTA work up
- LFTs:
    - ↓ Albumin mean ↓ calcium
    - Protein bound calcium can be ↓ but ionized calcium may be normal
    - ↑ALP does not differentiate between causes of rickets but it does indicate active rickets
- CPM:
    - If nutritional, Ca and PO_4 may be normal but PTH is ↑

  - Mg is important for PTH secretion
  - Phosphate levels do early morning
- PTH levels: important to differentiate between:
  - Ca & vit D def → PTH ↑
  - Hypophostaemic rickets → PTH normal
- Do both 25 and 1,25 vit D levels
- Urine:
  - Urine anion gap (Na+K) – Cl
  - Urine fractional excretion of phosphate > 15% indicates losing in urine. In some cases serum P may be low so there may not be adequate urine loss. In this case correct P and then test
  - Urine for metabolic screen: fructose / galactose
  - Urine for Ca and P
- Family hx (Phosphate): check mother's early morning levels (urine, serum)
- Screening tests for Fanconi's syndrome
- Serum Cu and ceruloplasmine (Wilsons)
- Leucocyte count of cysteine (in WBCs) → cystinosis
- X-linked hypophospataemic rickets (males) – FISH for PHEX gene mutation
- Cysteine crystals in eyes
- 25hrs fecal fat
- Bone biopsy

Treatment

Nutritional

  - 1 alpha calcidiol
  - Vitamin D
  - Calcium supplementation for 6-8 wks

Hypophosphataemic rickets

  - Phosphate & calcium supplementation
  - Active form of vitamin D (1,25) will ↑P absorption in gut and kidneys

Hypocalcaemia:

  - Calcium supplementation
  - 25 hydroxy vit D

NEPHROLOGY

NEPHROTIC SYNDROME

DEFINITIONS

1. **Nephrotic syndrome** – is a glomerular disease characterized by degenerative lesions of renal parenchyma and presents with:
   - Proteinuria >1g/m^2/24hr or >40mg/m^2/hr equivalent to 3 – 4 + on dipstix. The normal loss is upto 4mg/m^2/hr
   - Hypoproteinuria – albumin <25g/L
   - Oedema
   - Hyperlipidaemia
2. **Remission** – is said to occur when the urine is negative or trace for protein for at least 3 days
3. **Relapse** – is the occurrence of proteinuria measuring 2+ or more on 3 consecutive days in a pt who is in remission [heavy proteinuria persisting for 3-5 consective days]
4. **Frequently relapsing course** – is when a pt has >2 relapses within 6 months or 3 or more relapses within a year
5. **Steroid responsiveness** – a pt is said to be steroid responsive if he goes into remission within 8 weeks of starting treatment with a steroid
6. **Steroid resistance** – a pt is steroid resistant if there is no remission after 8 weeks on conventional doses of steroids
7. **Steroid dependence** – a pt is steroid dependent if he is unable to discontinue steroid use without experiencing a relapse
8. **Transient proteinuria** – may occure with an intercurrent infection in children with MCNS & is not considered as a relapse. Steroid therapy usually is rapidly effective for a true relapse

Common congenital causes of oedema

- Alport syndrome
- Congenital nephrotics
- TORCH (consider TORCH in all children under 1 yr)

Common conditions to rule out

- CCF
- Constrictive pericarditis → apex beat palpable, no visible veins
- Cardiomyopathy → no displacement of apex beat
- Chronic liver dx → hepatitis → signs of jaundice and clubbing
- Renal → nephrotic, nephritic

CLASSIFICATION OF THE NEPHROTIC SYNDROME

- Classification could be based on: aetiology, therapeutic response to steroids & histology

A). Aetiological classes of NS

- **Primary:** NS due to a primary glomerular dx e.g., IgA nephropathy
- **Secondary:** NS as part of another dx e.g., SLE, Hep B, HIV etc.

Causes of secondary nephrotic syndrome

1. Infections: P malariae, T pallidum, HBV, HIV, Salmonella, CMV (Dr Thula)
2. Toxins: Heavy metals (Lead, Hg), drugs e.g., captopril, penicillamine, trimethadone
3. Vasculitis: SLE, HSP, PAN, JDMS, JCA
4. Allergy: Bee stings, pollens
5. Malignancies: Lymphomas, leukemias, Wilms tumor
6. Miscellaneous: Renal vein thrombosis, constrictive pericarditis, amyloidosis, HUS, Alports syndrome

B.) Therapeutic classes of NS

1. Steroid sensitive
2. Steroid resistant
3. Steroid dependent
4. Frequently relapsing

C). Histological classification (is independent of the aetiology)

1. Minimal change NS (MCNS) – commonest amongest non-Africans
2. Membranous glomerulonephritis
3. Focal segmental glomerulosclerosis (FSGS)
4. Diffuse mesangial hypercellularity (DMH)
5. Mesangiocapillary glomerulonephritis

THE HISTOLOGIC TYPES: CLINICAL AND MICROSCOPIC FEATURES

5. **MCNS**

- 70-80% of cases, male:femal ratio 2:1, age <7yrs
- **Pathogenesis:** T-cell derived factor that causes podocytes damage and wiping out of foot processes
- **Typical MCNS is defined as:**
- **Clinical:** The commonest amongst non-African in RSA. It is typically a dx of toddlers often preceded by an URTI, a history of allergy or immunization. The proteinuria is selective i.e., low mwt (<68,000) molecules are lost. In typical MCNS there is absence of persistant haematuria, renal insufficiency, HTN and hypocomplementaemia. It normally responds to steroids. Pts who respond to steroid therapy have little risk of developing CRF.
- **Microscopically:** Renal tissue is normal on light microscopy and there are no deposits on immunofluorescence. On electron microscopy (EM) podocytes with effaced foot processes are seen (effaced mean wiped out).

2. MEMBRANOUS NEPHROPATHY

- 1% of children with NS on renal biopsy
- **Clinical:** The commonest in African children, adolescents &adults
    - Heamaturia is present in 50-80% pts at the onset and nearly all pts develop haematuria during the course of the dx
    - HTN and renal failure occur in the course of the dx
    - Poorly responds to steroids
    - It is the type commonly associated with immune complex deposits:
        - HBV, malaria, toxoplasmosis, syphilis
        - SLE, ITP,
        - Sickle cell dx (SCD)
        - Malignancies
        - Drugs: gold salts, penicillamine
- **Microscopically** characterized by diffuse subendothelial deposits and a thickened GBM. The deposits are mainly IgG, C3,IgM, IgA

NB: Black children if:

- They are HIV negative → most likely have MCNS
- If HBV positive → membranous nephropathy

3. FOCAL SEGMENTAL GLOMERULAR SCLEROSIS

- Sclerosis mean hardening from inflammation
- **Clinical:** It is dx of older children. Heamaturia, HTN occurs in 50%. They are likely to be steroid resistant, steroid dependent or frequently relapsing. Steroid resistance may be present initially or may develop after months or yrs. FSGS may evolve from MCNS or DMH. A circulating factor that increases glomerular permeability to albumin is found in some pts in FSGN.
- **Microscopically:** On light microscope sclerosis is focal i.e some of the glomeruli are spared. However EM reveals collapse of capillaries wrinkled GBM, sclerosis and vacuolation of podocytes which may be detached from the GBM. There are IgM and C3 deposits in the lesions.

4. DMH – diffuse mesangial hypercellularity

- **Clinically**: Proteinuria is insiduos and the other biochemical features of NS may be absent
- Heamaturia, HT, RF may occur
- Only 50% are steroid sensitive and a frequently relapsing coarse is common
- **Microscopically** – there is an increase in mesangial cells and matrix with or without scattered dense deposits

PATHOPHYSIOLOGY OF NEPHROTIC SYNDROME

1. PROTEINURIA

- Proteinuria is due to glomerular loss of protein into the urine. Glomerular damage could be either at 1 and /or 2 levels:
    - The glomerular capillary endothelium
    - The glomerular basement membrane
- At the capillary level there is loss of anion sites which normally repel the negatively charged albumin, hence keeping it within the lumen. The reduction in the anionic sites could be due to:
    - Loss of GBM sialoproteins
    - Congenital absence or poor development as in the congenital NS
    - Cationic substance that mops them up as in MCNS
- The cationinc substance is believed to be released by altered T cells. Therefore in MCNS low mwt negatively charged molecules are lost (**selective proteinuria**)
- At the GBM level there is an increase in the size of the pores which is due to immune complex deposition by a cytokine produced by an abnormal clone of T cells which directly damages the GBM. As a result the proteinuria is **non-selective**. In some diseases both mechanisms are operative

2. HYPOALBUMINAEMIA

- The hypoalbuminaemia is due to increased:
    - Urinary loss
    - Catabolism in the proximal tubule
    - Non renal losses through the GIT

3. OEDEMA

Oedema formation in the NS is multifactorial. The mechanisms involved are as follows:

- **Underfil theory:** urinary protein loss→ hypoalbuminaemia → reduced oncotic pressure → disruption of the Stirling forces → interstitial fluid leak → oedema → decrease in the effective circulating volume → activation of the rennin angiotensin system → elevated levels of aldosterone → increased sodium reabsorption in the proximal tubule. However not all pts have elevated rennin or aldosterone levels

- **Overfill hypothesis:** intrarenal defect in Na handling → reduced filtration to ANP → increased $_C$GMP phosphodiesterase activiry → reduced Na-K-ATPase activity → increased tubular reabsorption of Na → salt & water retention → oedema

- Children with nephrotic syndrome who are HIV infected may not present with oedema due to hypergammaglobulinaemia that may compensate for albumin (Prof Bhimma 11.05.201

4. THE HYPERLIPIDAEMIA

- Cholesterol, TGs, LDL, VLDL are all increased. The lower the albumin, the higher they are.

- The causes of hyperlipidaemia are:
    - Increased hepatic synthesis as a response to hypoalbuminaemia, low oncotic pressure and high viscosity at the sinusoidal level
    - Decreased clearance, lipase activity is decreased by about 30-60% in the NS

Basic investigations

- Urine dipstix and microscopy
- Urine protein/creatinin ratio: early morning specimen & define degree of proteinuria
- U/E, S albumin, S cholesterol
- Serum complement C3, C4
- Hep B & C serology
- HIV PCR
- Mantoux

MEDICAL MANAGEMENT OF NEPHROTIC SYNDROME

1. GENERAL MEASURES

- The parents & the child if old enough should be explained the implications of the diagnosis as regards to the chronicity & possible relapsing course
- Normal activity should be allowed, bed rest should not be enforced although it can induce a diuresis and decrease protein excretion

2. DIET

- A low salt diet – no added salt even during remission
- Fluids should be restricted to $\pm$ 75% of maintenance requirements during periods of oedema
- A normal protein intake of 3g/kg/day – supplements are for those who are malnourished

3. CONTROL OF OEDEMA

- Achieved by the use of diuretics and/or albumin infusions
    - **DIURETICS**
        - Maintenance diuretics: monitor haematocrit to prevent haemoconcentration
        - Diuretics are used in combination in order to produce a synergistic response example furosemide (in acute cases) plus a thiazide or spironolactone or amiloride. However diuretics may worsen the hypovolaemia and pre renal failure
    - **ALBUMIN INFUSIONS**
        - Indicated when serum albumin is <15g/ L. Each ml of 20% albumin attracts 4ml of fluid into the circulation. Dose: 0.5-1g/kg over 1hr followed by furosemide 2mg/kg halfway through the infusion, daily or 12 hourly for 3 days

    - Before albumin is infused make sure the BP is normal & no signs of CCF or pulmonary oedema because rapid shifts in fluids may lead to further decompensation
  - **CONTROL OF PROTEINURIA**
    - Captopril/enalapril and indomethacin decrease the proteinuria by 30-50% in steroid resistant NS. Monitor K and BP

4. CORTICOSTEROIDS

- Are contraindicated in Hepatitis B
- Are indicated for MCNS where they are thought to act by inhibiting the release of the cationic substance from the immune system. More than 95% of MCNS responds to steroids within 4-8 weeks, the majority within 2 weeks. However 63% of DMH and 30% of FSGS respond as well
- **Regimen:** Prednisone 2mg/kg/day in the morning (max 60mg/day) for 4 weeks and then tail off. The early morning dosing co-incides with the highest physiological cortisol secretion and also minimizes GH suppression. Once the urine is protein free for at least 3 days, ½ the dose should be given on alternate days for another 4 weeks
- **Complications of steroids:** obesity, HTN, osteopenia, DM, peptic ulcer dx, recurrent infections, cataracts. If C3 levels are low, a renal biopsy may be indicated before a trial of steroid therapy

5. OTHER IMMUNOSUPPRESSIVE AGENTS

- These are reseved for pts who are:
  - Steroid resistant
  - Persistently oedematous
  - Steroid dependent with steroid toxicity
  - Frequent relapsers
- The agents commonly used are:
  - **Cyclophosphamide** – as IV pulse therapy – 500mg/m^2/dose
    - Advantages – higher frequency of overall remission, longer duration of protein free days, lower cumulative dose than with oral therapy, fewer side effects
    - Side effects – **short term**: alopecia, heamorrhagic cystitis, chromosomal breaks, leucopenia, **long trem**: infertility, secondary malignancy
  - **Chlorambucil** – 1-2mg/kg/day orally
  - **Pulsed methyl prednisolone** – 30mg/kg IV daily for 3 days [Mandoza Regimen]
    - Side effects – cardiac arrhythmias, anaphylaxis, catarcats, osteoporosis, hypertension, metabolic complications, myopathy
  - **Cyclosporine A** – 5mg/kg/day
    - Side effects – nephrotoxicity, BM suppression, hypertrichosis, gum hyperplasia, hypomagnesemia

6. TREATMENT OF RELAPSES

- Relapses can be monitored at home by the parents or pts diarizing early morning dipstick heamturia. About 60% of pts with MCNS will relapse and ± 40% will have frequent relapses
- Relapses may occur because of:
  - non compliance
  - an intercurrent infection
  - a too low dose of miantiance corticosteroid
  - no apparent reason at all
- The **approach to relapses** is:
  - Firstly to treat any underlying infection if any since spontaneous remission may follow
  - If this does not induce a remission – the same prednisone regime as above is recommended until there is a remission
  - In frequent relapsers, a smaller dose is given (0.5-1mg/kg) on alternate days for a longer period in order to minimize toxicity
  - Pulsed methylprednisone is another alternative or if there is steroid resistance, cyclophosamide etc can be tried

7. TREATMENT OF HTN

Ac HTN: Beta blockers or Calcium channel blockers
Persistant HTN: ACE inhibitors

8. FULL IMMINIZATION

On remission ensure full immunization against pneumococcu, haemophlus influenzae

9. EARLY ANTIBIOTIC THERAPY

10. ADDITIONAL THERAPY UNDER PAEDIATRIC NEPHROLOGIST

- Levamisol 2.5mg/kg/d usually with tapering steroid therapy
- Calcinurine therapy: cyclosporine & Tacrolimus to spare steroids which are nephrotoxic
- Cyclophosphamide 2.5-3mg/kg/day or chlorambucil 0.2 mg/kg/d as stabilizing medication [both for max of 8-12 wks]
- In focal glomerulosclerosis: combination of chlorambucil 0.2mg/kg/d for max 12 wks & sirolimus 1mg/m2/d may be efficacious

11. PROTOCOL FOR STEROID RESISTANT NEPHROTICS/FREQUENT RELAPSERS: MANZOZA REGIMEN

- Methylprednisolone at 30mg/kg/dose as an infusion
- Methylprednisolone infusion **alternate days** x 6 doses
- Methylprednisolone infusion **weekly** x 8 doses
- Methylprednisolone infusion **2 times per month** x 4 doses
- Methylprednisolone infusion **monthly** x 16 dose
- Also requires to be on oral prednisone 1mg/kg alternate days orally

- While on this regimen you need to monitor for side effects:
    - HTN, osteoporosis, glucose intolerance, cushingoids features, arrythemai, myopathy and cataracts.
- Monitor U/E and albumin weekly, check urine dipstix, urine protein:creatinin cario during weekly infusions
- Methylprednissolone infusion: dose 30mg/kg in 200 ml normal saline over 2 hrs. Monitor PB strictly every 30 minutes during this infusion
- Mandoza protocol record need to be updated with each infusion

COMPLICATIONS OF NEPHROTIC SYNDROME & THEIR MANAGEMENT

- These are:
    - Renal complications
    - Recurrent infections
    - Thromboembolism
    - Failure to thrive
    - Tetany

1. RENAL COMPLICATIONS

- The renal complications of the NS are:
    - ARF – caused by hypovolaemia, nephrotoxicity or high interstitial pressure from oedema in the kidneys
    - End stage renal dx (ESRD)
    - HTN due to Na tretension (Prof Bhimma)
- The **treatment** of:
    - ARF is reduction of dietary protein
    - ESRD is dialysis or transplantation
    - HT is reduced sodium intake and antihypertensive medications

2. INFECTIONS

- Patients with NS are susceptible to recurrent infections especially:
    - Strep pneumonia
    - H influenza
    - E coli
    - Chicken pox
- The main mechanism underlying these infections are based on the secondary immunosuppression due to:
    - Corticosteroids and or cytotoxics
    - Low Ig levels because they lose them in the urine
    - Altered T cell activity (they have low CMI)
    - Defective opsonization because of an abnormality in the alternate C pathway, (factor B is lost in the urine)
- The treatment of infections is based on the following principles:
    - Routine immunization against childhood infections e.g., measles, DPT etc.
    - ZIG, MIG if there has been exposure
    - Hib, pneumovax, best done during a remission
    - Meticulous skincare

- Broad spectrum antibiotics PRN
- Polyvalent gammaglobulins if there is severe sepsis

3. THROMBOEMBOLISM (hyperco-agulable state: Renal VT, Pulm E)

- 5% of pts with NS are prone to both venous and arterial thrombosis
- Causes are multifactorial:
  - Thrombocytosis
  - High platelet and RBC aggregability
  - High fibrinogen levels and factors I, II, VII, VIII, X
  - Low anti-thrombin III – lost in urine
  - Low protein S – lost in urine
  - High – alpha 2 antiplasmin

  (Anticloting mechanisms see Ganong p543)
- **Treatment** – mobilize pt
- If thrombosis occurs heparin can be used but in higher doses because nephrotics have a decreased sensitivity. Aspirine and dipyramidole are not recommended
- Warfarine, reduced dose aspirine and dipyridamol can be used to reduce the risk of clot

4. FAILURE TO THRIVE

- Is caused by:
  - Anorexia,
  - Protein loss
  - High protein catabolism
  - Frequent infections
- **Treatment:**
  - Balanced diet
  - Calories
  - Vitamins
  - Minerals

5. TETANY

- Is caused by low levels of both protein bound and ionized calcium. Low calcium is caused by low intestinal absorption, low 25 hydroxycalciferol because the binding protein is lost in the urine
- **Treatment:**
  If a patient has tetany, rebreathing in a bag causes a temporary resp acidosis which shifts non ionized calcium, or give IV calcium gluconate

6. RICKETS: due to loss of vitamin D binding globulin

7. HYPOTHYROIDISM: due to loss of thyroid binding globulin

8. ANAEMIA: due to loss of transferrin

CONGENITAL NEPHROTIC SYNDROME

DEFINITION
Congenital nephrotic syndrome (CNS) is a NS that presents within the 1st 3/12 of life

CLASSIFICATION
- CNS can be:
  - Primary i.e., no known cause or
  - Secondary i.e., associated with other systemic dx
- The primary CNS is further subclassified into:
  - The Finnish type AR –characterised by cystic dilatation of the proximal tubules
  - Non Finnish type – includes diffuse mesangial sclerosis, MCNS, FGS

FINNISH TYPE CNS
- Babies are usually prems. SGA. The placenta is larger than normal (25-50% of the baby weight)
- Asphyxia is common. Fontanelles are large, nose small, ears are low set. Postural deformities of the knees and hips
- Feeding is poor and oedema starts in the 1st month
- Proteinuria, heamaturia, leucocyturia + glycosuria may occur
- Finnish type CNS is usually resistant to steroids

SECONDARY CNS could be associated with:
- Intra uterine infections
  - TORCH
  - Syphilis
  - HIV
  - Hepatitis B
- Gonadal dysgenesis
- Nail-Patella syndrome
  AD, hypoplasia or absence of patella, dystrophic nails, dysplasia of elbows and iliac horns, renal dx (benign nephropathy, microhaematuria, mild proteinuria). Some pts develop NS and mild HTN. Risk of development of ESRD

APPROACH TO A CHILD WITH CONGENITAL NEPHROTIC SYNDROME

Syndromes to look:

- Trisomi, Deny Drash, Lowe
- TORCH, Nail-Patella, congenital brain formations like Meckle-Gruber syndrome
- Features of syphilis
- Secondary causes need to be excluded before making diagnosis of CNS (TORCH, HBV, syphilis, toxo, malaria malariae, toxins, Hg)

Genetics

- Mutations in 1of 2 genes (NPHS1 & NPHS2) which encode the proteins Nephrine & Podocin
- Nephrine & Podocin are essential components of slit diaphragm of glomerular epithelial cells and play an essential role in the normal functioning of glomerular filteration barrier (Nelson p2195)

Major features of Finnish type

- Dilatation of proximal tubules
- Mesengial hypercellularity
- Glomerulosclerosis

Presentation

- Massive proteinuria, large placenta, large oedema,
- In-utero detection: increased alpha fetoproteins, DNA analysis, especially indicated in families at risk of Finnish type

Differential diagnosis

- Secondary NS
- Diffuse mesengial sclerosis
- DMS

Denys Drash syndrome

- Wilims tumor + male pseudohermaphroditism
- Caused by mutation in WT1on chromosome 11

Associations of CNS

- CVS: ESM of pulmonary stenosis 2/6 in 25% cases of CNS
- May occur as an isolated dx or as part of Denys Drash syndrome
- Pathological finding: progressive sclerosis of glomerular mesengium
- Clinical picture → rapid loss of renal function → ESRD months to yrs

Forms common in CNS on histology

- DMS
- FSGS

- Minimal change

Investigations

- Urine dipstix- proteinuria massive – if trace or +1 may be albumin depleted. Then test by giving albumin ivi then repeat dipstix
- Urine protein: creatinin ratio
- TSH, T4
- Lipids profile: triglyceroid + cholesterol (usually normal)
- U/E: renal functions usually normal. Urea may be reduced due to reduced albumin and proteins
- US kidneys: increase in size + echogenic
- FBC: infections → they are immunocompromised
- Ask hx of mother about SLE (screen mother)

Management

- CNS: poor prognosis
- Oedema:
    - Albumin + diuretics sometimes need x 3 doses per day with lasix ½ way through and at the end
    - Plasma
- Nutrition:
    - Protein 3-4g/kg/day
    - Calories 130 kcal/kg/day
- Prevent infections
    - Vaccinate → EPI
    - Varicella zoster
- Treat infections vigorously even if you cannot find focus of infection as they are immunocompromised
- Reduce protein loss: ACE inhibitors + indomethacine
- Treat hypothyroidism: eltroxin
- If no improvement → unilateral nephrectomy
- If this does not help → bilateral nephrectomy and put the child on dialysis
- Renal transplant

ETIOLOGY OF HAEMATURIA

Microscopic haematuria: when there are >3-5 RBCs in HPF in freshly voided & centrifuged urine

URINE ANALYSIS

Red urine with no blood on dipstix:

- Ingested foods
- Medications

Red urine with blood on dipstix – no blood on microscopy (MS):

- Presnce of free Hb or myoglobin: haemoglobinuria, myoglobinuria
- Acute iv haemolysis, DIC
- Rhabdomyolysis – sec to crush injury
- Burns, myositis
- Asphyxia

Red urine, blood on dipstix, no RBC casts

- Urinary tract bleeding from a site beyond renal tubules
- Sickle cells, or bleeding disorders
- Sternous exercise
- Trauma
- Renal parenchymal dx (normal RBCs or no casts does not exclude glomerular dx)

Red urine, blood on dipstix & MS with RBC casts

- Variety of glomerular diseases: HSP, PAN, SLE, WG
- Immune injury → PSAGN
- Inherited → Alport syndrome
- Vascular injury → acute tubular or cortical necrosis
- Child with haematuria with casts and proteinuria <1g/m2/day → nephritis

Non glomerular causes

- Non urinary regional bleeding: anal fissure, trauma, infection
- UTI: Bacterial, viral (adenovirus), schistomiasis (S. Haematobium),
- Sickle cell, bleeding disorder
- Calculi, hypercalciuria, hydronephrosis – reflux or obstruction, renal cysts, tumors (Wilms, Rhabdomyosarcoma), renal artery or vein thrombosis

For other causes see Coovadia p604 & investigations → see B Nelson p757

GLOMERULONEPHRITIDES

CLASSIFICATION (Forfar p626)

Primary glomerulonephritis

- Immune complex
  - Postinfectious
  - IgA nephropathy – Berger's dx
  - Mesangiocapillary
  - Idiopathic membranous
- Anti GBM-AMGN (glomerulobasement membrane-antibody mediated GN)
- Unknown aetiology
  - MCNS
  - Focal segmental glomurosclerosis (FSGN)

Secondary to systemic diseases

- Immune mediated
  - HSP, SLE, PAN (polyarteritis nodosa)
  - Wegeners granulomatosis
  - Systemic infections:
    - Hep B, HIV
    - SBE, syphilis, malaria
    - Shunt nephritis
- Hereditary disorders
  - Alports syndrome
  - Thin basement membrane dx
  - Nail patella syndrome
  - Sickle cell anaemia
- Metabolic disorders
  - IDDM
  - Cryoglobulianaemia
  - Amyloidosis

CLINICAL PATTERNS OF GN

Glomerular dx may present as:

- An acute nephritic syndrome
  - Heamaturia
  - Proteinuria
  - Varying degrees of renal impairment
  - Volume overload
- A nephrotic syndrome
  - Massive proteinuria (+3, >3g/L)
  - Hypoalbunianemia
  - Oedema
  - Hyperlipideamia (urine microscopy → fatty casts + free fat droplets
- Asymptomatic heamaturia and /or proteinuria

1. POST STREPTOCOCCAL GLOMERULONEPHRITIS

- **Etiology:** inciting antigen may be exogenous or endogenous.
    - Exogenous is seen in PSGN
    - Infective organism is most commonly group A strepoccocus or others like:
        - Pneumococcal & staphylococcal organisms
        - Viruses: measles, mumps, chicken pox, HBV, HCV
        - Endogenous: SLE, membranous nephropathy type
- Incubation period 5-21 days (av10 day)
- An immunologic reaction to the bacteria is mediated by activation of complement (M protein type 49) which leads to proliferative GN
- There is glomerular deposition of immune complexes resulting in diffuse proliferation of & swelling of resident glomerular cells & frequent infilteration of leukocytes especially neutrophils.
- **Pathophysiology:**
- Oedema + cola colored urine → reduced GFR + increased Na absorption at distal conv tubules → increase plasma volume → suppression of plasma renin → renal insufficiency → oliguria +HTN → heart failure + encephalopathy
- Typical features of immune complex dx are
    - Glomerular deposits of IgG & complement on GBM
    - Hypocomplementaemia
    - Haematuria
    - Hypertension
    - Oedema

Management: admit all pts with ac nephritis

General measures:

- Strict bed rest, sit upright if pulm oedema
- Observe daily wt
- Vitals, BP 4 hrly
- Strict intake/output monitoring
- Test tube urine displayed
- Restrict fluids to insensible losses 15ml/kg/day until no longer volume overload – then increase to normal
- Restrict Na intake – no chips, nicknaks, added salt
- Restrict proteins if urea >20mmol/L
- Treat infection: PenVK or erythromycin if allergic
- Pulmonary oedema: Lasix 1-2 mg/kg/d
- Morphine 0.1mg/kg/d
- Hypertension: can increase Lasix upto 5 mg/kg/d if no response. If BP more than 140/100 give Nifedipine 5mg/d – monitor BP hrly until stable.hydralazin 0.1-0.8mg/kg/d
- Renal failure: catheterize – monitor, Na, Urea/electrolytes. If oliguria → Lasix

- Discharge home if macroscopic haematuria disappears, if oedema resolved, BP is normal and U/E is normal or falling rapidly, on normal diet, Lasix & antihypertensives
- Follow-up: three monthly at district hospital to check urine dipstix & BP. Refer back to renal clinic if haematuria persists >1 yr, HTN and renal impairement beyond acute phase

2. MESANGIOCAPILLARY GLOMERULONEPHRITIS

It is an immune complex dx also called as membranoproliferative GN

Clinical presentation

- Gross heamaturia or microscopic heamaturia
- Proteinuria
- Hypertension
- Serum C3 may be depressed (because of the classical pathway activation in type I and the alternative pathway activation in types II and III).

The differentiation from PSGN:

- Serologic evidence of a streptococcal infection in PSGN (ASOT, anti hyaluronidase and anti DNA ase B)
- Pts with PSGN usually recover within 8 weeks of onset, C3 returns to normal within 8 weeks and proteinuria and heamaturia clear within 6 months but in MCGN reduced amounts of C3 persists beyond 8 weeks
- A renal biopsy should be considered in those with an atypical course or if nephritic illness is complicated by nephrotic syndrome

There are 3 histologic types

- **Type I** – marked mesangial cell proliferation, increase in mesangial matrix, thickening of the glomerular capillary walls and duplication of the GBM, producing a double contour
- **Type II –** dense deposit disease, resembles type I on light microscopy but has extensive dense depostis in the GBM and C3 is always present on IF (immunoflurances) along segments of glomerular, tubular and capsular basement membrane
- **Type III** – variable

3. IgA NEPHROPATRHY – BURGERS DISEASE

Characteristic immunoflorescent deposition of IgA principally in mesengium

- Normal C3
- Raised IgA levels (20%)
- Microscopic haematuria or proteinuria or both
- Affects children and young adults
- Episode occurs in 1-2 days of non specific URTI
- Haematuria lasts for several days – subsides & recurs every few months
- Often associated with loin pain

Pathogenesis

- Abnormality in IgA production & clearance
- Levels increase due to increased production in marrow in response to respiratory & GIT infections
- Abnormality in glycosylation of IgA reduces clearance and further increases IgA deposition in mesengium → activates alternate complement pathway → initiates glomerular dx

4. MEMBRANOUS GN

Characterized by presence of subepithelial immunoglobuline containing deposits along GBM

- Slow progressive dx
- Age 30-50 yrs
- Microscopically:
    - Diffuse thickening of GBM
    - Subepithelial deposits
    - Effacement of foot processes
    - Presence of spikes
- Etiology
    - Idiopathic 85%
    - Secondary: infections – HBV, syphilis, schistosomiasis, malaria
    - Malignant tumors
    - SLE
    - Exposure to inorganic salts (gold, Hg)
    - Drugs like penicillamin, captopril, NSAIDS

5. HENOCH SCHONLEIN PURPURA

Is a small vessel IgA mediated vasculitis characterized by:

- Palpable purpura over the buttocks & lower extremities. In severe cases oedema of the scalp and upper extremities may precede the skin lesions. The rash recurs in 10% of cases
- Colicky abd pains with or without bloody diarrhea. It may br complicated by an ileo-ileal intussusseption
- Polyarthritis involving mainly the knee and ankle joints
- Nephritis – the majority are mild with <1% developing severe renal disease. Renal biopsy shows deposition of IgA and electron dense deposits in the mesangium and along the capillary wall
- **Cause:** Unknown but may be secondary to various infections and drugs
- **Lab findings:** are non-specific. Serum IgA may be elevated in 50% of pts. There may be haematuria, proteinuria. C3 and ASOT are normal
- **Treatment:** Supportive in mild cases. NSAIDs $\pm$ steroids in severe cases

6. POLYATERITIS NODOSA

PAN is a longitudinal medium sized vasculities of the kidneys, CNS, muscle and viscera

Clinical presentation

- There are 2 varieties
  - A systemic variety which presents with
    - Fever
    - Painful skin nodules, ulcers, gangrene
    - Muscle pain and tenderness
    - Glomerulonephritis
    - Myocarditis and coronary artery involvement
  - A cutaneous variety which presents with tender S-C nodules, high fever, arthralgias and myalgias without major organ involvement

Diagnosis

- There are no serological markers – no association with ANCA (Robbins p366)
- Diagnosis is clinical, based on criteria:
  - Weight loss >4 kg
  - Livedo reticularis
  - Testicular pain or tenderness
  - Myalgias, weakness or leg tenderness
  - Mononeuropathy or polyneuropathy
  - Diastolic BP >90 mmHg
  - Elevated BUN >40mg/dl or creatinine >1.5mg/dl
  - Hepatitis B virus
  - Ateriographic abnormailities – aneurysms or occlusions of the visceral arteries
  - Biopsy of small or medium sized artery containing PMN's

7. WEGENERS GRANULOMATOSIS

WG is a necrotizing granulomatosis small vessel vasculitis that occurs in all ages and often involves upper & lower airway and kidneys. (Nelson p1049).

- Characterized by nasal discharge from ch sinusitis with mucosal ulceration & bone distruction, hamoptysis & dyspnea, haematuria & proteinuria due to GN (late manifestation)
- Diagnosis by:
  - Lab findings of high ESR, CRP, leukocytosis, thrombocytosis and anaemia
  - CT high resolution of chest – interstitial densities consistant with Vasculitis or pulm haemorrhage and granulomas
  - A positive cytoplasmic staining anti-neutrophil cytoplasmic antibody (C-ANCA)
- DD: sarcoidosis and TB (absent ANCA) & Churg-Strauss synd (hx of asthma and circulating eosinophilia)
- Complications: intrasinus lesions can invade orbit, unilateral deafness, subglottic stenosis and pulmonary haemorrhage
- **Treatment:** steroids, cyclophosphamide & methotrexate.

8. ALPORTS SYNDROME

- Is the commonest hereditary nephritis. The majority are x linked dominant, others autosomal recessive possible autosomal dominant as well (Forfar p360).
- Upto 20% of patients are new mutations.
- The defect is an abnormality of the alpha 5 chain of collagen IV an important constituent of the GBM (GBM is largly composed of type IV collagen which is made up of hetrotrimmers of alpha 3, 4 & 5 type collagen. This form of collagen is crucial for normal function of lense, chochlea and glomerulus. Mutation in any one of the alpha chain results in defective hetrotrimmer aseembly and thus dx manifestations of Alport syndrome)

Clinical presentation

- Sensori-neural hearing loss
- Lense dislocation, posterior cataract, corneal dystrophy
- Asymptomatic microscopic or macroscopic heamaturia
- ESRD in the 2nd or 3rd decade of life.
- Females usually have a normal life span and only minimal hearing loss

Diagnosis is based on:

- Clinical findings
- Family history
- EM shows splitting and weaving of the densa producing the so called basket weave pattern / lattice work appearance

IMPORTANT COMPLICATIONS OF NEPHRITIS (Coovadia p607)

- Fliud volume overload
- Pulmonary oedema & CCF
- HTN and hypertensive encephalopathy – may have sizures
- Rapidly progressive GN (usually crescentic on biopsy)
- ARF & CRF

Posterior leukoencephalopathy - may have seizures (rapid change of BP and dysragulation of BBB may cause cerebral oedema

ESTABLISHING THE CAUSE

- Black children – if HBV –ve – otherwise most likely are meb GN
- Age <1yr >7yrs
- NS with heamaturia, HT, RF, persistently low C
- Congenital or secondary glomerular dx
- Steroid resistance

INVESTIGATIONS

1. The FBC
   - Anaemia-may suggest the presence of collagen vascular dx, malignancy or SCD
   - Thrombocytosis- observed in primary NS
   - Thrombocyopaenia – may suggest SLE, HUS
   - Leucopaenia may suggest SLE wheras leucocytosia may suggest infection
2. For Group A beta hemolytic streptococcus:
   - Throat swab ASOT
   - Anti-DNase B
   - Anti-hyaluronidase
   - Total C3/C4
3. U/E (renal functions), LFTs (albumin, associated hepatitis)
4. TPHA or FTA: to rule out syphilis
5. HBs and e antigens
6. ANF, anti DNA titres to rule out SLE
7. HIV – PCR or ELISA
8. Other important investigations in the RSA context
   - Mantoux
   - CXR: To rule out TB in view of the anticipated prolonged immunosuppressive Rx
   - Urine for MCS

DOCUMENTING COMPLICATIONS

1. Establishing the degree of renal impairment

- Sodium: Usually low because of increased reabsorption in the proximal tubule, pseudohyponatreamia associated with hyperlipideamia
- Potassium: Is usually normal if elevated one should suspect a renal tubular defect in potassium secretion as occurs in ARF or lupus nephritis
- Urea and creatinine: Usually high in untreated NS, but are normal during remission
- ABG's: Hyperchloraemic metabolic acidosis with a normal anion gap suggests RTA and occurs in FSGS

2. Other biochemical derangements

- T3 +T4 may be low because of decreased binding. However free T4, T3 TSH and T3/T4 ratios are normal
- Ionized serum calcium may be low because of decreased binding of vit D metabolites
- Total plasma calcium must be corrected for the level of albumin that is:
  - Total plasma calcium = Measured calcium + $\frac{40 - \text{albumin}}{40}$
- Serum IgG and IgA are reduced because they are lost in the urine. However serum IgM is raised because of an abnormality of T-cell function that regulates IgM coversion to IgG. IgE levels have been reported raised in MCNS

For comments & suggestions: muhammad.ghuman@kznhealth.gov.za