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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• Cardiac anomalies: (e.g., tetralogy of Fallot, VSD, ASD) • Facial abnormalities: Cleft palate Micrognathia (small lower jaw) and/or retrognathia Dysplastic ears High and broad nasal bridge Investigations • Chest X-ray shows absence of the thymic shadow. • Low levels of serum calcium (Ca2+) and parathormone (PTH) • ↓ Absolute T-lymphocyte count • Delayed hypersensitivity skin testing • Fluorescence in situ hybridization (FISH) → Detection of 22q11.2 deletion MRCP-part-1-May 2019 exam: In a patient having DiGeorge syndrome, which infection is he most at risk from, secondary to his immune system dysfunction? Cryptococcus neoformans (T-cell dysfunction →↑↑risk from recurrent viral and fungal infections)

Wiskott-Aldrich syndrome (WAS) Definition • Wiskott-Aldrich syndrome (WAS) is defined as an X-linked hereditary disorder associated with adaptive and innate immunodeficiency, micro-thrombocytopenia, eczema, and an increased risk of autoimmune disorders and malignancy. Pathophysiology • "Loss-of-function" mutation in WASP gene (X-linked recessive inheritance) → combined B- and T-cell dysfunction and thrombocytopenia Epidemiology: occurs primarily in males Features • Classic tetrad

1. Purpura (bleeding diathesis)
2. Eczema (high risk of atopic disorders)
3. Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)
4. Increased risk of autoimmune diseases and hematological malignancies (e.g., lymphoma, leukemia) Investigations • Thrombocytopenia with small platelets • Low IgM and IgG levels • ↑ IgE and IgA • Genetic analysis (confirmatory test): mutated WASp gene Prognosis • The disease has variable penetrance, which means that life expectancy can range from 6 - 30 years. Wiskott-Aldrich syndrome: Classic tetrad of:
5. Purpura (bleeding diathesis)
6. Eczema (high risk of atopic disorders)
7. Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)
8. ↑Risk of autoimmune diseases and hematological malignancies

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Complement deficiencies C3 deficiency is associated with recurrent bacterial infections, C5 deficiency is more characteristically associated with disseminated meningococcal infection Deficiencies of the classical complement pathway such as C1 and C4 deficiencies are strongly associated with the development of systemic lupus erythematosus; deficiencies of the alternative pathway, such as C3 and C5–9, are associated with increased risk of recurrent pyogenic infections. Overview • Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body. • Complement proteins are involved in chemotaxis, cell lysis and opsonisation. • Most of complement deficiencies are inherited in autosomal recessive fashion; the exception being properdin deficiency, which is usually described as having an X-linked inheritance pattern. C1 inhibitor (C1-INH) protein deficiency • causes hereditary angioedema • C1-INH is a multifunctional serine protease inhibitor • probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues C1q, C1rs, C2, C4 deficiency (classical pathway components) • predisposes to immune complex disease • e.g. SLE, Henoch-Schonlein Purpura, vasculitidies • mechanism complement activity is associated with clearance of circulating immune complexes If immune complexes are not cleared, they undergo tissue deposition where an inflammatory process is triggered, leading to SLE C3 deficiency • causes recurrent bacterial infections • Deficiencies of C3 is more commonly associated with haemolytic uraemic syndrome C5 deficiency • predisposes to Leiner disease • recurrent diarrhoea, wasting and seborrhoeic dermatitis C5-9 deficiency • encodes the membrane attack complex (MAC) • particularly prone to Neisseria meningitidis infection • Absent classical and alternate pathway activity Membrane attack complex (MAC) • Formed by C5b, C6, C7, C8, and multiple copies of C9 complement proteins on pathogen cell membranes • Function →lyses pathogens • Inhibited by CD59 This exists on body cells to protect them from MAC.

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 paroxysmal nocturnal haemoglobinuria, results in red cells that lack CD59. These red cells can, therefore, be lysed by MAC. Decay-accelerating factor (DAF) deficiency is associated with Paroxysmal nocturnal haemoglobinuria (PNH). Diagnosis • CH50 assay screening test MRCPI-part-1-jan-2017: Post splenectomy what type of immunodeficiency is occurs? Humoral Post splenectomy there is increased susceptibility to H. Influenzae, N. Meningitidis and Strep pneumonia which are encapsulated organisms due to the loss of splenic macrophages which are part of the humoral response. MRCPUK-pat-1-May 2019 exam: A 23-year-old man is admitted with sepsis. Blood cultures are reported as Neisseria gonorrhoeae. Which complement protein is the patient most likely to deficient in?
• C5-9

Hereditary angioedema Overview • Hereditary angioedema is an autosomal dominant condition associated with low plasma levels of the C1 inhibitor (C1-INH) protein. • C1-INH is a multifunctional serine protease inhibitor Pathophysiology • Deficiency of C1 esterase inhibitor leads to persistent activation of the classical complement pathway and C4 levels are frequently low secondary to activation and consumption. ↓C1 inhibitor allow C1 to act on C4 and C2 • Mechanism of attacks :

uncontrolled release of bradykinin resulting in oedema of tissues. Investigation • C1-INH level is low during an attack • Low C2 and C4 levels are seen, even between attacks. • Serum C4 is the most reliable and widely used screening tool • Angioedema does not readily cause a rise in mast cell tryptase.

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Features • Painless, non-pruritic swelling of subcutaneous/submucosal tissues urticaria is not usually a feature attacks may be proceeded by painful macular rash • May affect upper airways, skin, genital or abdominal organs (can occasionally present as abdominal pain and vomiting due to visceral oedema) • Triggers include stress, infection and menstruation Management • Acute: IV C1-inhibitor concentrate (1000-1500 units given intravenously over 20-30 min), fresh frozen plasma (FFP) if this is not available • Prophylaxis: Anabolic steroid, synthetic androgen: Danazol may help Aminocaproic acid Complication • If treatment fails to normalise the C4 levels and they remain persistently low, these patients are at an increased risk of developing SLE. Other Causes of angioedema • Bradykinin-mediated angioedema Hereditary angioedema (inherited C1 inhibitor deficiency) Acquired angioedema (acquired C1 inhibitor deficiency) Often associated with lymphoproliferative diseases and B-cell malignancies ACE inhibitor-induced (rarely ARB-induced): impaired bradykinin breakdown Can occur within days to 2 years after starting ACE inhibitor • Histamine-mediated angioedema (mast cell-mediated angioedema) Usually coexist with urticaria Salicylate- and/or aspirin-associated angioedema Moxonidine is a centrally acting antihypertensive and is associated with angioedema • Idiopathic angioedema: Possible triggers: cold, heat, stress, and exercise

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Granulomatous inflammation Definition • A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg ,TB), immune-mediated diseases, and foreign bodies. • A granuloma is a collection of macrophages: giant cells as a nidus of chronic inflammation Mechanism • Macrophages →↑cytokine secretion (eg, TNF) → formation of epithelioid macrophages and giant cells Types of granuloma and causes • Caseating granulomas Granulomas with central necrosis Found in infections e.g., tuberculosis, fungal infections, tertiary syphilis, Bartonella henselae (cat scratch disease) • Noncaseating granulomatous inflammation Granulomas without central necrosis Found in immune-mediated diseases (e.g., sarcoidosis, Crohn disease), sarcoidosis, vasculitis, and foreign body exposure TNF-α is important for maintaining the granuloma. It is essential to test patients for latent TB before initiating anti-TNF therapy because the drug causes breakdown of the granuloma and can result in disseminated TB.

Third edition Notes & Notes For MRCP part 1 & 11 By Dr. Yousif Abdallah Hamad Basic sciences Genetics Updated

Chapter 16

Basic sciences Genetics

Autosomal dominant conditions Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions: • some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant • some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive The following conditions are autosomal dominant: • Achondroplasia • Acute intermittent porphyria • Adult polycystic disease • Antithrombin III deficiency • Ehlers-Danlos syndrome • Familial adenomatous polyposis • Hereditary haemorrhagic telangiectasia • Hereditary spherocytosis • Hereditary non-polyposis colorectal carcinoma • Huntington's disease • Hyperlipidaemia type II • Hypokalaemic periodic paralysis As an autosomal dominant condition, two affected parents can expect: • 1 in 4 chance of an unaffected child • 1 in 2 chance of an affected heterozygous child • 1 in 4 chance of an affected homozygous child. Which disease demonstrates autosomal co-dominant inheritance? □ Alpha-1-antitrypsin deficiency *type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease Notes & Notes for MRCP
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• Malignant hyperthermia • Marfan's syndromes • Myotonic dystrophy • Neurofibromatosis • Noonan syndrome • Osteogenesis imperfecta • Peutz-Jeghers syndrome • Retinoblastoma • Romano-Ward syndrome • Tuberose sclerosis • Von Hippel-Lindau syndrome • Von Willebrand's disease*

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Achondroplasia Aetiology • Mutation in fibroblast growth factor receptor 3 gene (FGFR3) → reduced endochondral ossification □ activation of fibroblast growth factor receptor 3 on chromosome 4, resulting in inhibited chondrocyte proliferation. • autosomal dominant • The homozygous form is usually fatal. Epidemiology • Most common type of skeletal dysplasia and disproportionate short stature (1:40,000 children worldwide affected) Risk factor • The incidence increases with paternal age. Pathophysiology • Epiphyseal growth cartilage fails, • there is normal bone formation and repair. □ Therefore, NO increased risk of fracture. Features becomes obvious within the first year with disparity between a large skull, normal trunk length and short limbs. • short stature • short limbs (rhizomelia) with shortened fingers (brachydactyly) □ The fingertips may only come down to the iliac crest, and the shortness of the limbs is often most marked proximally. □ short stature due to shortening of the limbs, but spinal length is maintained. □ The limbs appear broad with deep creases. • large head (Macrocephaly) with frontal bossing • midface hypoplasia with a flattened nasal bridge • 'trident' hands • lumbar lordosis • Normal intelligence Complications • Small foramen magnum □ compression of the cervical medulla • Spinal canal stenosis and radiculopathy (of the lower back) □ low back and leg pain, □ paresthesias, dysesthesia, □ incontinence • Secondary scoliosis • Recurrent otitis media • Cardiopulmonary complications (due to a small chest wall) Diagnostics • X-ray □ It may be diagnosed radiographically at birth, □ Lateral skull □ midface hypoplasia, □ frontal prominence □ pelvis

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 narrow in anteroposterior diameter with deep sacroiliac notches and short iliac wings. Spine progressive narrowing of the interpedicular distance from top to bottom (reverse of normal). abnormally narrow interpedicular distance → spinal canal stenosis; scoliosis Extremities bones are short and broad; short fingers metaphyseal irregularity, flaring in the long bones, late-appearing irregular epiphyses. Management • medical Early administration of growth hormone (1–6 years) • Surgical corrections: spinal stenosis, secondary scoliosis, genu varum, foramen magnum decompression

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Osteogenesis imperfecta (“brittle bone disease”) Pathophysiology • Autosomal dominant mutation in COL1A1 or COL1A2 genes → ↓ synthesis of normal type I collagen → impaired bone matrix formation (osteogenesis) Features • Growth retardation • Skeletal deformities, brittle bones, and recurrent fractures from minimal trauma • Blue sclerae due to visible choroidal pigment. • Progressive hearing loss secondary to otosclerosis • Brittle, opalescent teeth (dental imperfections) due to a lack of dentin formation. Types • type 1:The most common, and milder form. • Type II: most severe form; lethal perinatally or within the first year Diagnostics • DNA test • Ultrasonography before birth and radiographic skeletal survey afterwards (fractures, callus, deformities) • Bone or skin biopsy type 1 collagen mutation Therapy • No cure available • Bisphosphonates; decrease the risk of fractures • Surgery for functional improvement Individuals with osteogenesis imperfecta can't BITE: Bones (recurrent fractures), I (“eye” = blue sclerae), Teeth (dental abnormalities), Ears (hearing loss). MRCPUK-part-1-May-2009 exam: A pregnant woman is known to have polycystic kidney disease. What is the chance her child will also have the disease?
 50% (Polycystic kidney disease is usually inherited in an autosomal dominant fashion and hence 50% of her children will be affected, regardless of gender)

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Down's syndrome (trisomy 21) Epidemiology and genetics • the most common autosomal abnormality Risk of Down's syndrome with increasing maternal age Age (years) Risk

1 in 1,500

1 in 800

1 in 270

1 in 100

1 in 50 or greater One way of remembering this is by starting at 1/1,000 at 30 years and then dividing the denominator by 3 (i.e. 3 times more common) for every extra 5 years of age Cytogenetics Mode % of cases Risk of recurrence Non-disjunction 94% 1 in 100 if under mother < 35 years Robertsonian translocation (usually onto 14) 5% 10-15% if mother is translocation carrier 2.5% if father is translocation carrier Mosaicism 1% • The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much higher. • Down syndrome have one of the two karyotypes:

1. 47,XX,+21 (trisomy 21): more common
2. 46,XY,der(14;21): characterized by the presence of two normal chromosomes 21, one normal chromosome 14 and a product of Robertsonian translocation between chromosomes 14 and 21 (der(14;21); der stands for derivative).

The general risk of trisomy 21 increases with maternal age. This does not, however, apply to translocation trisomies

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Features • face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face • flat occiput • single palmar crease, pronounced 'sandal gap' between big and first toe • hypotonia • congenital heart defects (40-50%, see below) • duodenal atresia can be diagnosed by U/S at gestation double bubble sign • Hirschsprung's disease Associations • ↑↑ risk for developing acute myeloid leukemia (AML) (approximately 1-2% of children with Down syndrome develop AML, the great majority < 5 y) rather than acute lymphoblastic leukemia (ALL), which is a more common form of leukemia in children. • Other haematological disorders associated with Down's syndrome include: Fanconi's anaemia, Patients with learning disabilities may be prone to lead poisoning due to pica. Cardiac complications • 50% of children with Down's syndrome have a cardiac defect. • multiple cardiac problems may be present • endocardial cushion defect (c. 40%, also known as atrioventricular septal canal defects) • ventricular septal defect (c. 30%) • secundum atrial septal defect (c. 10%) • tetralogy of Fallot (c. 5%) • isolated patent ductus arteriosus (c. 5%) Later complications • subfertility: Males are almost always infertile due to impaired spermatogenesis. Females are usually subfertile, and have an increased incidence of problems with pregnancy and labour • learning difficulties • short stature • repeated respiratory infections (+hearing impairment from glue ear) • acute lymphoblastic leukaemia • hypothyroidism • Alzheimer's • atlantoaxial instability Diagnosis Screening tests (Prenatal) • Combined test (first trimester) (11–13 weeks) Maternal serum ↑ Beta human chorionic gonadotropin (β-hCG) ↓ Pregnancy-associated plasma protein A (PAPP-A) To remember the most important features associated with Down syndrome, think of the 5 A's: Advanced maternal age, duodenal Atresia, Atrioventricular septal defect, AML/ALL, early onset of Alzheimer disease.

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 Ultrasound Nuchal translucency; increases due to the large amount of fluid collecting behind the neck Short neck, thickened nuchal fold Absent or hypoplastic nasal bone Shortened middle phalanges of the fifth digits with clinodactyly Shortened long bones (humerus, femur) • Quadruple test (second trimester) (15–18 weeks) ↓ Free estriol ↓ Alpha-fetoprotein (AFP) ↑ Inhibin A ↑ β-hCG Diagnostic tests (confirmatory test) • Prenatal → Fetal karyotyping Chorionic villus sampling (9–14 weeks) Amniocentesis (15–22 weeks) Percutaneous umbilical cord sampling (18–22 weeks) • Postnatal → Chromosome analysis

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Noonan’s syndrome Overview • Relatively common, autosomal-dominant inherited disorder. • Caused by activating mutations in multiple genes in the Ras/mitogen-activated protein kinase (RAS-MAPK pathway). • The most commonly implicated gene is PTPN11. on chromosome 12 • Often thought of as the 'male Turner's', • In contrast to Turner's syndrome, the karyotype is normal • The majority of patients lead normal lives Feature • features similar to Turner's syndrome: short stature, webbed neck, chest (pectus) deformity widely-spaced nipples, pectus carinatum and excavatum, • characteristic features: cardiac: (occurs in 50% to 80%) typically, pulmonary valve stenosis atrial septal defect (ASD) occasionally hypertrophic cardiomyopathy easy bruising or bleeding (due to coagulation factor deficiency or platelet dysfunction), coagulation problems: factor XI deficiencies facial features, triangular-shaped face hypertelorism (increased distance between the eyes) In the quadruple test, hCG and Inhibin A are both HIgh up (↑) and Estriol and αfEtoprotein are both dEficient (↓).

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 downslanting eyes vivid blue or blue-green irides low-set, posteriorly rotated ears ptosis Boys frequently present with cryptorchidism and manifest delayed puberty. learning disabilities, Mild cognitive impairment is found in up to 33% Intellectual development may be delayed, but by adulthood intelligence is normal in ⅔ of patients.

Autosomal recessive conditions Autosomal recessive conditions are 'metabolic' - exceptions: inherited ataxias Autosomal dominant conditions are 'structural' - exceptions: hyperlipidaemia type II, hypokalaemic periodic paralysis The following conditions are autosomal recessive: • Albinism • Ataxia telangiectasia • Congenital adrenal hyperplasia • Cystic fibrosis • Cystinuria • Familial Mediterranean Fever • Fanconi anaemia • Friedreich's ataxia • Glycogen storage disease Notes & Notes for MRCP
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Two copies of the defective gene (one inherited from each parent) are required in order to be born with the disorder. Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions: • some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant • some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive • Haemochromatosis • Homocystinuria • Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick •

Mucopolysaccharidoses: Hurler's • PKU • Sickle cell anaemia • Thalassaemias • Wilson's disease

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MRCPUK-part-1-May 2012 exam: A man diagnosed as having hereditary hemochromatosis. His wife is not a carrier. What is the chance his child will develop haemochromatosis?
 0% (Haemochromatosis is an autosomal recessive condition. If one of the parents has haemochromatosis (i.e. is homozygous) and the other is not a carrier/affected, then all the children will inherit one copy of the gene from the affected parent and hence will be carriers)

Ehlers–Danlos syndrome (EDS) • Ehlers-Danlos syndrome is a disorder of faulty collagen synthesis most commonly affecting collagen type III and V. • Inheritance patterns and type of collagen affected vary (can be autosomal dominant or recessive) • Collagen deficiencies in Ehlers-Danlos syndrome are often caused by problems with crosslinking. • Hypermobile Ehlers-Danlos syndrome (EDS) is the most common of 13 subtypes. Most hypermobile people are not aware of the fact and assume that everyone is as flexible as they are. Most cases of hypermobile EDS, are inherited in an autosomal dominant manner. associated with hypermobile joints, but skin features are much less prominent Systemic features may include increased propensity to asthma, mild valve regurgitation and gastrointestinal (GI) symptoms, including constipation and hiatus hernia. • The most severe form of Ehlers-Danlos syndrome is the vascular type. deficiencies in type III collagen. Type III collagen also known as reticulin, and is found primarily in granulation tissue, artery walls, skin, intestines and the uterus. involves vascular and organ rupture due to type III collagen deficiency. • The classical type of Ehlers-Danlos syndrome has deficiencies in type V collagen. in which joint and skin manifestations predominate associated with much more severe dermatological features, including hyperelastic skin that splits easily and marked propensity to bruising. • Kyphoscoliotic EDS is usually inherited in autosomal recessive fashion. Features Cardiovascular • Features of heart valve defects (particularly mitral valve prolapse) • Features of aneurysms/dissections of the iliac, splenic, renal arteries, or the aorta • Berry/saccular aneurysms of the cerebral arteries → features of subarachnoid hemorrhage Musculoskeletal • Joint hypermobility with tendency to dislocate • Skeletal abnormalities (e.g., scoliosis) • features of chronic pain syndrome and marfanoid habitus Skin • Tendency to bruise easily • Skin hyperextensibility • Frequent skin lacerations and poor skin healing (e.g., following surgery) Other • Hernias • Features of organ rupture (e.g., shock, local pain), especially in vascular EDS The classic presentation of EDS involves hyperextensible skin, joint hypermobility, and a tendency to bleed easily.

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Elbow region of a female patient of Ehlers-Danlos syndrome: The skin of the elbow is hyperelastic (cutis hyperelastica), but rapidly returns to its initial position when released. Diagnosis • Definitive diagnosis for all subtypes of EDS, except hypermobile EDS, can be made by molecular genetic testing. • The genetic basis of hypermobile EDS remains unknown and the diagnosis is made by

clinical criteria only. • A baseline echocardiogram with views of the aortic arch and aorta and regular reevaluations should be obtained to evaluate for mitral valve prolapse and any signs of aortic enlargement. Prognosis • Life expectancy is typically normal with the exception of vascular EDS, which has a reduced life expectancy of ~50 years.

Pseudoxanthoma elasticum (PXE) • inherited condition (usually autosomal recessive*) connective tissue disorder involves the elastic fibres of the eye, skin and cardiovascular system. *there are reports of autosomal dominant inheritance in a minority of cases • caused by mutations in the ABCC6 gene lack of functional ABCC6 protein leads to ectopic mineralization that is most apparent in the elastic tissues of the skin, eyes and blood vessels. Features • Eye retinal angioid streaks due to dystrophic calcification of Bruch's membrane Visual loss can occur by infarction of the visual pathways and is likely to explain the chronic changes of optic disc atrophy • Skin 'plucked chicken skin' appearance - small yellow papules on the neck, antecubital fossa and axillae The first clinical sign • Cardiac mitral valve prolapse, increased risk of ischaemic heart disease Due to loss of elastic tissue, patients have an increased incidence of mitral regurgitation, aortic regurgitation and aortic dissection.

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• Gastrointestinal haemorrhage • CNS Cerebral ischaemia in PXE is caused by small vessel occlusive disease. Intracranial aneurysms Subarachnoid and intracerebral haemorrhages Progressive intellectual deterioration Mental disturbances, and Seizures.

Phenylketonuria (PKU) Overview • Autosomal recessive condition • Caused by a disorder of phenylalanine (an essential amino acid) metabolism. usually due to defect in phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine . In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase. • The gene for phenylalanine hydroxylase is located on chromosome 12. • The incidence of PKU is around 1 in 10,000 live births. • High levels of phenylalanine lead to problems such as learning difficulties and seizures. • The sequence of phenylalanine metabolism is the following: phenylalanine →tyrosine →LDopa →dopamine →norepinephrine →epinephrine. the neurological symptoms are most likely caused by a reduction in which neurotransmitters? Norepinephrine Features • usually presents by 6 months e.g. with developmental delay, seizures, typically infantile spasms • child classically has fair hair and blue eyes • learning difficulties. Even with dietary treatment some degree of cognitive impairment is seen • Microcephaly, prominent maxilla, growth retardation and wide-spaced teeth are found in untreated children.

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• Eczema • partial albinism due to decreased tyrosine production. • 'musty' odour to urine and sweat secondary to phenylacetate, a phenylketone Diagnosis • Diagnosis of classic PKU requires raised Phe levels, increased urinary Phe metabolites and normal cofactor (tetrahydrobiopterin) concentrations. plasma levels of tyrosine are difficult to measure, and have diurnal variation. Whilst the levels are often low in patients with PKU, the levels can be normal depending on what time of the day the sample is taken and whether or not the patients are being treated. • Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism • hyperphenylalaninaemia • phenylpyruvic acid in urine Management • Low phenylalanine and high tyrosine diet Prognosis • Excellent with normal life expectancy diagnosed early and blood phenylalanine (phe) levels remain within the therapeutic range.

Alkaptonuria The black discoloration of sclera and urine becoming black on standing should alert you to the likelihood of Alkaptonuria. Pathophysiology • Autosomal recessive disorder of phenylalanine and tyrosine metabolism • Caused by a deficiency of homogentisic acid oxidase responsible for the degradation of homogentisic acid produced from phenylalanine and tyrosine. • Accumulation of homogentisic acid causes pigmentation of the urine, sclera and connective tissues. • Alkaptonuria is generally a benign and often asymptomatic condition. Features • Pigmented sclera • Urine turns black if left exposed to the air • Deposition in the joints causes cartilage pigmentation (ochronosis) and degeneration. Patients develop arthritis at 40 years of age. intervertebral disc calcification may result in back pain The knees and spine are commonly affected. The sacroiliac joint may be spared. • Renal stones • Homogentisic acid is a reducing agent, therefore it gives a false positive Glucostix test but normal Clinitest. Treatment • High-dose vitamin C • Dietary restriction of phenylalanine and tyrosine

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X-linked recessive • The abnormal gene is carried on the X chromosome, and in the carrier female, the normal allele on her other X chromosome protects her from the disease. Since the male does not have this protection, he manifests the disease. • only males are affected. An exception to this seen in examinations are patients with Turner's syndrome, who are affected due to only having one X chromosome. • Females only occasionally show mild sign of disease • X-linked recessive disorders are transmitted by heterozygote females (carriers) and maleto-male transmission is not seen. • Affected males can only have unaffected sons and carrier daughters. • heterozygous female carrier   50% of male children are affected 50% of female children are carrier • The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen. • Many of the inherited eye disorders such as retinitis pigmentosa and ocular albinism are inherited in an x-linked recessive pattern. • The following conditions are inherited in a X-linked recessive fashion: Androgen insensitivity syndrome Becker muscular dystrophy Colour blindness Duchenne muscular dystrophy Fabry's disease G6PD deficiency Haemophilia A,B Hunter's disease Lesch-Nyhan syndrome Nephrogenic diabetes insipidus Ocular albinism Retinitis pigmentosa Wiskott-Aldrich syndrome Fragile X syndrome • The following diseases

have varying patterns of inheritance, with the majority being in an X-linked recessive fashion: Chronic granulomatous disease (in > 70%) X-linked conditions: Duchenne/Becker, haemophilia, G6PD X-linked recessive conditions - there is no male-to-male transmission. Affected males can only have unaffected sons and carrier daughters.

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Basic sciences Genetics What is the most common genetic disorder ? Sex-linked disorder The most common genetic disorder is actually a relatively minor one, red-green colour blindness, which is seen in 2–4% of men. Other examples of more significant sex-linked disorders include haemophilia A and B.

X-linked dominant disorders No carrier (the carrier of a defective gene associated with a disorder, will have the disorder) affected woman Half of the daughters and sons are affected male will have worse symptoms than female (because women carry two X) affected father all his daughters are affected but none of his sons. • The gene responsible for a genetic disorder is located on the X chromosome, and only one copy of the allele is sufficient to cause the disorder when inherited from a parent who has the disorder. • X linked dominant disorders are rare (for example, vitamin D-resistant rickets). • They affect both sexes but females more than males.

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 Males can only get an X chromosome from their mother whilst females get an X chromosome from both parents. As a result, females tend to show higher prevalence of X-linked dominant disorders because they have more of a chance to inherit a faulty X chromosome. • Homozygous mother →All children are affected. • An affected mother with the trait →half the sons and half the daughters inherit the disorder • when the mother alone is the carrier ; she herself will have the disorder. 50% Of her daughters and sons will have the disorder, 50% will be unaffected. • Affected females will transmit the condition to 50% of their children, whether male or female. • When the father alone is the carrier of a defective gene associated with a disorder, he too will have the disorder. 100% Of his daughters will have the disorder, since all of his daughters will receive one copy of his single X chromosome. none of his sons will have the disorder; sons do not receive an X chromosome from their father. affected father all his daughters are affected but none of his sons.

Vitamin D-resistant rickets Overview • Vitamin D-resistant rickets is a X-linked dominant condition affected female will transmit the disease to 50% of her sons and 50% of her daughters. affected male will transmit the condition to all of his daughters but none of his sons. • usually presents in infancy with failure to thrive. • caused by impaired phosphate reabsorption in the renal tubules Features • failure to thrive • normal serum calcium, low phosphate, elevated alkaline phosphotase • x-ray changes: cupped metaphyses with widening of the epiphyses Diagnosis • made by demonstrating increased urinary phosphate Management • high-dose vitamin D supplements • oral phosphate supplements

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Mitochondrial diseases • Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA Characteristics: Mitochondrial inheritance has the following characteristics: • inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote • all children of affected males will not inherit the disease • all children of affected females will inherit it • generally, encode rare neurological diseases • poor genotype: phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy) Histology • muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria Examples • Leber's optic atrophy Cyanocobalamin (a form of B12) should be avoided as it may lead to blindness in Leber's disease patients. • MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes • MERRF syndrome: myoclonus epilepsy with ragged-red fibres generalised myoclonus (60%), Mitochondrial diseases follow a maternal inheritance pattern

 epilepsy,
 optic atrophy (20%), short stature (10%), ataxia, cognitive decline encephalopathy (EEG findings of generalised slow waves) sensorineural hearing loss impaired glucose tolerance. • sensorineural hearing loss Myoclonic epilepsy with ragged red fibres (MERRF) A young patient presenting with cognitive impairment developing after a period of normal development, seizures, myoclonic jerks, Wolff-Parkinson White syndrome and worsening vision (consistent with optic atrophy). Diagnosis → (MERRF), which is a mitochondrial DNA disorder diagnosed by →ragged red fibres on muscle biopsy.

Kearns-Sayre syndrome Overview • mitochondrial DNA mutation. • onset in patients < 20 years old Features • external ophthalmoplegia Ptosis • retinitis pigmentosa • heart conduction defect
• sensorineural hearing loss is almost universal in those who survive into the fourth decade of life; this may not be fully corrected with hearing aids. • Other associated features:
 cerebellar ataxia, raised cerebrospinal fluid (CSF) proteins, proximal myopathy. short stature
 multiple endocrinopathies including diabetes mellitus, hypoparathyroidism, and Addison disease. Kearns-Sayre syndrome: Mitochondrial inheritance Onset < 20-years-old Triad of: External ophthalmoplegia Retinitis pigmentosa and Heart block.

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Diagnosis • Muscle biopsy may reveal ragged red fibers. • Muscle histochemistry reveals deficiency of cytochrome c oxidase (mitochondrial respiratory chain enzyme). Prognosis • Patients rarely live beyond their 40s and there are no therapeutics currently available.

Kallman's syndrome Overview • Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism. • It is usually inherited as an X-linked recessive trait. • Caused by failure of GnRH-secreting neurons to migrate to the hypothalamus → gonadotrophin releasing hormone (GnRH) deficiency • May arise due to abnormalities of the KAL-1 or KAL-2 gene (encoding anosmin-1 and FGF1). • There is isolated gonadotrophic deficiency (may be evidenced by a normal prolactin). • The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty Incidence • 1 in 10,000 males • More common in men: male to female ratio of 4:1. Features • Hypogonadotrophic hypogonadism Sex hormone levels are low LH, FSH levels are inappropriately low/normal Lack of development of secondary sexual characteristics Primary amenorrhoea. • Infertility In male individuals: cryptorchidism and low sperm count In female individuals: primary amenorrhea • Cryptorchidism (Cryptorchidism is more suggestive of Kallman's than Klinefelter's syndrome) Cryptorchidism is the absence of one or both testes from the scrotum (undescended testis). • Anosmia present in 75% (Lack sense of smell) due to failure of the olfactory bulb to develop, leading to loss of gonadotropin releasing hormones. • Patients are typically of normal or above average height • No mental retardation • Delayed puberty: (e.g., absent thelarche in female individuals, decreased growth spurt) Kallman's – LH & FSH low – normal Klinefelter's – LH & FSH – raised

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• Associated disorders Renal agenesis Cleft lip/cleft palate Visual defects : colour blindness Deafness Diagnosis • Diagnostic test →Fluorescent in situ hybridisation (FISH) is currently the best means of a genetic diagnosis
• Absent olfactory bulbs are present on 75% of MRI scans in these patients. The appearance on cerebral MRI →Absent olfactory bulbs Treatment • For a male who begin a relationship with a woman Pulsed (NOT Continuous) GnRH treatment is needed to restore LH and FSH release. It needs to be continued for as long as fertility is required. As natural GnRH release is pulsatile, continuous therapy fails to lead to LH and FSH release. Once his family is complete, switching to testosterone therapy may be more convenient for him. Although Testosterone supplementation will restores secondary sexual characteristics, it doesn’t restore fertility and is therefore not appropriate here. FSH can be used to induce fertility, but it is less effective than pulsed GnRH therapy.
• If fertility is not required, there is no need to stimulate spermatogenesis with (GnRH) or gonadotropins; only testosterone replacement is required. • LH can be used in conjunction with FSH to induce fertility in women with Kallmann syndrome. • For a woman who wants to start a family: HCG to drive production of gonadal steroid hormones, FSH to drive ovulation, harvesting of eggs, and IVF. This process is most effective in achieving successful pregnancy.

Klinefelter's syndrome Overview • Klinefelter's syndrome is associated with male phenotype and 47, XXY karyotype • the commonest form of which is XXY, is the result of chromosomal non-

dysjunction; as such, it does not follow a mendelian pattern of inheritance. Klinefelter's? - do a karyotype

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• it is the most common chromosomal disorder associated with male hypogonadism and infertility. • Incidence: between 1 in 500 and 1 in 1000. • The rate of chromosomal non-dysjunction increases with increasing maternal age and increasing paternal age, each parent contributing 50% of the risk. Around 60% of Klinefelter cases do not survive the fetal period. • has no specific genetic pattern of inheritance chances of inheriting the disorder < 1% Features • often taller than average • lack of secondary sexual characteristics • small, firm testes • infertile, azoospermia • gynaecomastia
 increased incidence of breast cancer (20 times higher than a normal male). • elevated gonadotrophin levels (↑↑LH/FSH) due to testicular failure Leydig cell dysfunction ↓testosterone ↑LH ↑estrogen. dysgenesis of seminiferous tubules ↓ inhibin B ↑ FSH. • Low testosterone levels • Low HDL cholesterol, elevated triglyceride ,normal or increased (LDL) • increased cardiovascular risk due to lipid abnormality. • decrease libido • decrease bone mineral density increased risk of osteoporotic fractures. Investigation • Diagnosis is by chromosomal analysis • the most appropriate investigation in suspected cases FSH, LH Both FSH and LH are raised in Klinefelter syndrome, and elevation would be a strong pointer to confirming the underlying diagnosis. more useful than Testosterone (wouldn’t indicate whether the defect was at the level of the pituitary or the testes) Treatment → Testosterone • Testosterone is known to improve bone mineralization and is the treatment of choice

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Turner's syndrome Overview • affects around 1 in 2,500 females. • caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes. • denoted as 45,XO or 45,X Features • short stature • shield chest, widely spaced nipples • webbed neck • cardiac defects: bicuspid aortic valve (15%), coarctation of the aorta (5-10%) hypertension and systolic murmur Turner's syndrome - most common cardiac defect is bicuspid aortic valve

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Revision #1
Created 2026-01-06 17:52:42 UTC by Omar Ayman
Updated 2026-01-06 17:52:42 UTC by Omar Ayman