041 - Chapter 6

041

Chapter 6

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology

Haemodialysis (HD) Assessment of haemodialysis adequacy: The adequacy of haemodialysis session is best measured by : • 'Clearance' is used to indicate dialysis adequacy, and most commonly the clearance of urea is used. Clearance is the ratio of removal rate to blood concentration. Removal rate can be measured by sampling blood on either side of the dialyser and multiplying the difference by the inflow rate. Clearance is the removal rate divided by the inflow concentration. However, this only provides a measure of dialysis at one point in time. • The adequacy of an entire haemodialysis session is best measured by the fall in solute concentration from before dialysis to after. This is calculated using complex equations and is expressed as Kt/V. The current recommendation for adequate dialysis for three treatments per week are a Kt/V of 1.2. • (the 'urea reduction ratio').A more crude assessment of the adequacy of dialysis obtained by noting the magnitude of the decrease in blood urea concentration • It is standard practice in the UK to take biochemical and haematological measurements before and after haemodialysis sessions at regular intervals (monthly in hospital HD patients and at least 3 monthly in home HD patients). Adequate HD is indicated by: pre-dialysis serum bicarbonate levels of 18-24 mmol/L, potassium 4.0-6.0 mmol/L, phosphate 1.1-1.7 mmol/L, calcium and albumin within normal range. Pre and post- dialysis values: • . A high pre-dialysis or inter-dialysis blood pressure may be related to: excessive sodium and water ingestion during the inter-dialysis period or a high dialysate sodium level, • A high post-dialysis blood pressure may reflect inadequate achievement of dry weight. Volume and blood pressure are linked and it is therefore important to optimise ultrafiltration and dry weight to control blood pressure. A patient’s dry weight is their normal weight when they are not fluid overloaded, also called euvolemia The rate of ultrafiltration depends upon the porosity of the membrane and the hydrostatic pressure of the blood, which depends upon blood flow. This is very effective in removal of fluid and middle-sized molecules, which are thought to cause uremia. • Weight gain between dialyses of more than 4.8% is associated with increased mortality. • The combination of high pre- and post-dialysis blood pressure, and high pre-dialysis potassium, indicate that the patient is receiving inadequate dialysis. Both procedural issues (insufficient blood flow rate, dialysis time and frequency and needle size) and access issues should be addressed.

 If these fail to improve the situation a different dialysis modality should be considered, such as more frequent or sustained haemodialysis. • It is recommended that pre-dialysis haemoglobin concentration should be maintained between 100-120 g/L. If his haemoglobin below the recommended level for a dialysis patient, you need to measure haematinics initially prior rather than jumping in with EPO treatment. Many haemodialysis patients are iron deplete, and in these cases intravenous iron is indicated rather than EPO in the first instance. Adverse effects of dialysis • Modem techniques of dialysis preclude chances of vitamin D or calcium deficiency, fluid and electrolyte imbalance or risk of viral hepatitis • protein-calorie malnutrition is the most common problem associated with haemodialysis seen in up to 50% of patients Dietary restriction of foods with high phosphate content (milk, eggs and cheese), decreased protein intake,anorexia, nausea and vomiting, may all contribute to this condition Complications of rapid haemodialysis • Disequilibrium syndrome: Caused by cerebral oedema, resulting from the rapid shifts of uraemic toxins associated with too-rapid haemodialysis in a severely uraemic patient characterized by weakness, dizziness, headache, and in severe cases, mental status changes. The diagnosis is one of exclusion; a prime characteristic of this syndrome is that it is nonfocal. Long-term haemodialysis • associated with carpal tunnel syndrome this is due to beta-2 microglobulin deposition • Cardio-vascular disease is the commonest cause of death (50%) in dialysis patients • Carnitine deficiency Patients on chronic hemodialysis may have carnitine deficiency. Carnitine is essential for the transport of long-chain fatty acids from the cytosol into the mitochondria. chronic hemodialysis carnitine deficiency Impaired mitochondrial transport of long-chain fatty acids Cardiomyocytes and skeletal muscle cells extensively use fatty acids as a fuel. Carnitine deficiency leads to: accumulation of long-chain fatty acids in the cytosol of cardiomyocytes (resulting in cardiac fatty change and cardiomegaly) accumulation of long-chain fatty acids in the cytosol of skeletal muscle cells (resulting in muscle cramps). Treatment is via L-carnitine administration.

Nephrology

Line-related infection A patient with a tunnelled haemodialysis catheter who develops a fever on dialysis should be considered to have line-related infection until proven otherwise. • The most common organisms for line-related sepsis are gram-positive bacteria, namely S. aureus. • Blood cultures should be taken from the line and peripherally, and if the same organism is growing from them both, this strongly suggests the line is the source of the infection. • Indications of Catheter removal : Staphylococcus aureus bloodstream infection non-staphylococcus aureus catheter-related bloodstream infection in the following circumstances: Severe sepsis Haemodynamic instability Endocarditis Evidence of metastatic infection, or Persistence of bacteraemia after 48-72 hours of effective antibiotics. • Treatment Methicillin-resistant Staphylococcus aureus (MRSA) infection vancomycin is the drug of choice Dialysis amyloidosis Aetio-pathogenesis • Occurs due to the failure of clearance of B2-microglobulin This protein, the light chain of class-1 HLA antigens, is usually freely filtered at the glomerulus but is not cleared by cellulose-based dialysis membranes • There is resulting amyloid deposition within the synovium Clinical features: Amyloid deposition within the synovium results in: • clinical syndrome of median nerve compression • pain and stiffness in multiple joints Treatment & Prognosis • The syndrome resolves

slowly after renal transplantation, • some benefit is seen in switching patients to dialysis with a biosynthetic dialysis membrane Complications: • gastrointestinal haemorrhage caused by amyloid deposition around submucosal blood vessels

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Peritoneal dialysis • Peritoneal dialysis (PD) is a form of renal replacement therapy. It is sometimes used as a stop-gap to haemodialysis or for younger patients who do not want to have to visit hospital three times a week. • The majority of patients do Continuous Ambulatory Peritoneal Dialysis (CAPD), which involves four 2-litre exchanges/day. Complications: • Peritoneal dialysis-associated peritonitis • sclerosing peritonitis • Adynamic bone disease (ABD)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Peritoneal dialysis-associated peritonitis • Causes: The most common cause coagulase-negative staphylococci such as Staphylococcus epidermidis (40-50% of cases). another common cause Staphylococcus aureus • Diagnosis is made by peritoneal fluid cell count (neutrophils above 100/ml).(White cell count

> 100/mm3 in PD fluid sample) PD fluid neutrophil percentage of greater than 50% is in keeping with PD peritonitis. • Treatment intraperitoneal antibiotics (vancomycin) And oral quinolone (Before culture results are received). the initial treatment of choice would be intraperitoneal antibiotics. initial antibiotic regimes should cover Gram positive (including MRSA) and Gram-negative organisms. Give intra-peritoneal vancomycin and gentamicin Intravenous antibiotics would be preferable if the clinical condition worsened despite intraperitoneal antibiotics, Recurrent Staph, epidermidis peritonitis may necessitate removal and replacement of the peritoneal dialysis catheter due to chronic colonisation Adynamic bone disease (ABD) (low bone turnover) • Definition: (ABD) is a variety of renal osteodystrophy characterized by reduced osteblasts and osteoclasts, no accumulation of osteoid and markedly low bone turnover (↓bone formation and resorption). • Distinguish ABD from the second low-turnover form, i.e. osteomalacia: In ABD: Both the rate of collagen synthesis by osteoblasts and the subsequent mineralization of bone collagen are subnormal. there are few or no osteoblasts In osteomalacia: mineralization defect exceeds the defects in bone formation, resulting in a relative osteoid excess. Bone alkaline phosphatase (BAP) is the single most useful biochemical parameter for the assessment of bone formation. ↑↑BAP exclude ABD elevations of BAP along with total AP may be seen in severe osteomalacia. • Risk factors & Causes: overtreatment of secondary hyperparathyroidism associated with CKD (ABD is, at least in part, often iatrogenic) commonly CKD patients on dialysis, either peritoneal or hemodialysis ↑ in CAPD compared to haemodialysis Especially prevalent in diabetic patients on peritoneal dialysis ↑ in age of dialysis patients Aluminum overload Serum aluminium levels

> do not correctly reflect body aluminium stores and do not correlate well with signs of aluminium toxicity. desferrioxamine (DFO) test increases the diagnostic accuracy High calcium load Low PTH levels Vitamin D over-treatment (eg : alfacalcidol) High prevalence of diabetes mellitus • Pathophysiology: basically in CKD: PTH serum levels are higher than normal

 bone tissue is resistant to PTH PTH serum levels decrease beyond relatively low levels, which would be considered normal in the general population. So that a relative reduction of PTH low turnover state. • Complications: (pain, fracture,↑ Ca+) bone pain increased incidence of hip fracture hypercalcaemia as the bone loses its capacity to buffer serum calcium • Treatment: currently follows two principles:

1. reduce calcium and vitamin D load Stop calcium-containing phosphate binders and replace with non-calcium-, non-aluminium-containing phosphate binders Assess oral dietary calcium intake and reduce to <2000 mg/day Reduce or stop active vitamin D compounds Lower dialysate calcium to 1.25 mmol/L or below Avoid bisphosphonates, strontium and fluoride administration
2. restore PTH activity • Follow- up Changes of bone markers, such as bone-specific alkaline phosphatase, over time, may be suitable indicators for the assessment of therapeutic effects. Other complications of peritoneal dialysis • Worsening of diabetic control: dialysis fluid contains a high glucose patients with diabetes may require significantly more diabetes treatment to reduce their blood glucose once dialysis is commenced • Worsening of abdominal hernias: due to the large fluid volume expansion and should be surgically repaired • Stomas adhesions: Stomas may be associated with significant adhesions and changes within the abdominal cavity making catheter placement impossible Contraindication of continuous ambulatory peritoneal dialysis (CAPD): • Colostomy. increase the risk of peritonitis • Recent or prospective abdominal surgery Complex abdominal surgery and resultant extensive adhesion damage the peritoneal membrane (peritoneal fibrosis) and lead to compartments within the peritoneum. Simple abdominal surgery, however, does not preclude peritoneal dialysis; examples include cholecystectomy, appendectomy or caesarian section. May 2013 exam: A patient on Ambulatory Peritoneal Dialysis (CAPD). Feels generally unwell with abdominal pain and fever. Which organism is most likely to be responsible for this presentation? Staphylococcus epidermidis

Renal transplant Hyperacute graft rejection is due to preexistent antibodies to HLA antigens and is therefore IgG mediated

Some basic points on the HLA system • class 1 antigens include A, B and C. Class 2 antigens include DP, DQ and DR • when HLA matching for a renal transplant the relative importance of the

HLA antigens are as follows DR > B > A • Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection? HLA-C Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection; specifically, HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection of renal transplant. Types of Transplants: • Autografts: same individual acts as both donor and recipient. • Isografts: donor and recipient are genetically identical (twins). • Allografts: donor and recipient are genetically dissimilar but belong to the same species (the commonest). • Xenografts: donor and recipient belong to different species (between animal and human). • Orthotopic transplants: the transplanted part is placed in its normal anatomical location. • Heterotopic transplants: the transplanted part is placed in different anatomical location. Graft survival 1 year 10 years Cadaveric transplants 90% 60% Living-donor transplants 95% 70% Hyper acute rejection (minutes to hours) • due to pre-existent antibodies against donor HLA type 1 antigens (a type II hypersensitivity reaction) and is therefore IgG mediated • rarely seen due to HLA matching • antigen-antibody complexes activate the complement system causing massive thrombosis in the capillaries avascularization of the graft.

Renal transplant HLA matching DR is the most important

Post-operative problems • ATN of graft • vascular thrombosis • urine leakage • UTI

Chapter 6

Nephrology • the kidney is most susceptible to hyperacute rejection; the liver is relatively resistant, possibly because of its dual blood supply, but more likely because of incompletely understood immunologic properties. Reasons for deterioration in renal function soon after a renal transplant: • Hyperacute rejection (which usually occurs in hours) • Acute tubular necrosis, and • Surgical complications (renal arterial or venous thrombosis and ureteric stenosis). In the presence of a dropping urine output and rising creatinine, an urgent ultrasound scan should be obtained to exclude any mechanical obstruction of the renal tract before considering other options. Acute graft failure (< 6 months) • Approximately 25% of transplant patients will have at least one episode of rejection mostly between days 7 and 21, and less commonly up to three months post-operation. • usually due to mismatched HLA. Cell-mediated (cytotoxic T cells) • other causes include cytomegalovirus infection Although CMV infection would not cause a sudden deterioration in renal function • Doppler ultrasound studies may show a sharp deterioration in graft perfusion, and kidney biopsy will show invading lymphocytes penetrating the tubular basement membrane, causing tubulitis. • It is often clinically silent, with only a sharp rise in serum creatinine pointing towards the diagnosis. • may be reversible with steroids and immunosuppressants Chronic graft failure (> 6 months) • both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy) • caused by recurrence of original renal disease (MCGN > IgA > FSGS) Recurrence of renal pathologies post-renal transplantation:

1. Membranoproliferative GN: 40-90% recurrence rate, type 2 much greater than type 1).
2. FSGS: 40%.
3. Membranous GN: 30%. Differentiate between acute cellular rejection and CMV Onset Feature Renal function Acute cellular rejection Commonly between days 7 and 21 often

clinically silent Sudden sharp rise in serum creatinine CMV Usually seen after four weeks Risk factors of chronic rejection include: • number of previous acute rejection episodes • presence of anti-HLA antibodies • anti-endothelial antibodies • CMV infection • dyslipidaemia • hypertension • functional mass of the donor kidney, and • delayed graft function (a clinical manifestation of ischaemia/reperfusion injury). Notes & Notes for MRCP By Dr. Yousif Abdallah Hamad

Systemic feature (pulmonary, GIT and Retinitis). Gradual rise in serum creatinine

Type of transplant rejection Hyperacute rejection Acute rejection Chronic rejection Frequency • < 1% • 50% • 50% Onset after transplantation • < 48 (usually within minutes to hours) • < 6 months (usually within days to weeks) Pathophysiology • Preformed antibodies against class I HLA → activation of complement system and adhesion to granulocytes → thrombosis of vessels → graft ischemia • T-lymphocyte induced cellmediated and/or humoral immunity Clinical findings • Intraoperative assessment: swelling of the organ as soon as perfusion is restored • Pain in the graft region • Graft edema • Fever and deterioration of general condition • In kidney transplants: ↑ BP and RFT; ↓urine output Diagnosis • Biopsy: small vessel thrombosis and graft infarction • Biopsy (confirmatory test) Prevention • Preoperative cross- matching, ABO grouping and HLA matching • Post-transplant immunosuppressive therapy Treatment • Graft removal • Change or increase dosage of immunosuppressive therapy Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

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> 6 months (usually after a few years) • Irreversible intimal fibrosis and obstruction of vessels • Slow, progressive loss of organ function • Biopsy Kidney: Glomerular sclerosis Heterogenous mononuclear aggregates± antibody deposition Heart: accelerated coronary artery disease C4d staining indicates humoral graft rejection Liver: vanishing bile duct syndrome Negative C4d staining indicates cellular rejection • Irreversible process with no known prevention • Graft removal, and re-transplantation

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology

Graft versus host disease (GVHD) presents with liver abnormalities, significant diarrhoea and skin changes. Definition • damage to the host as a result of a systemic inflammatory reaction induced by T lymphocytes present in the graft Etiology • Allogenous hematopoietic stem-cell transplantation • Small bowel transplantation • Transfusion of non-irradiated blood products Products implicated in cases of transfusion associated GVHD include: Non-irradiated whole blood Packed red blood cells Platelets Fresh non-frozen plasma Granulocytes The following have not been implicated: Frozen deglycerolised red blood cells FFP and Cryoprecipitate

Types of graft-versus-host disease Acute graft-versus-host disease Chronic graft-versus-host disease Onset • < 100 days after transplantation •

> 100 days after transplantation Pathophysiology • Donor T lymphocytes react with the recipient's organs Clinical presentation • Pruritic or painful maculopapular rash • Nausea, vomiting, diarrhea, and/or cramping abdominal pain • Hepatic dysfunction: jaundice Diagnostics • CBC: anemia, thrombocytopenia, leukope nia • ↑ALP • Confirmatory test: biopsy of skin, rectum, or liver Prevention • Antithymocyte globulin • Cyclosporine and one of the following: Methotrexate Mycophenolate mofetil Treatment • Optimize GvHD prophylaxis (e.g., cyclosporine levels) • Corticosteroids < 50% skin involvement: topical steroids Involvement of the GI tract, liver, or > 50% of skin: systemic steroids ± topical steroids Notes & Notes for MRCP
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• Mostly unknown • Scleroderma-like and lichenoid skin changes • Sicca syndrome: xerophthalmia, xerostomia, dry pruritic skin • Chronic enteritis (similar to inflammatory bowel disease): bloody diarrhea, abdominal pain, weight loss • Hepatic dysfunction: jaundice • Bronchiolitis obliterans: chronic cough, wheezing, and dyspnea that is not responsive to bronchodilator therapy
• Myasthenic symptoms • polymyositis: weakness, muscle pain • Spirometry: obstructive lung disease • Confirmatory test: biopsy of the skin, oral cavity, liver, or lung • First-line: corticosteroids
• Second-line : cyclosporine and increased corticosteroid dose

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology

Post-transplant problems Cytomegalovirus (CMV) infection Renal transplant + infection CMV • Epidemiology Over 50% of renal transplant patients have a significant infection within the first 12 months of having a renal transplant. • Risk factors Two main factors determine whether a patient will develop CMV infection after transplantation : Whether the donor or recipient harbours a latent virus capable of reactivation after transplantation At the time of transplant, the CMV-serological status of the donor and recipient are noted. the highest risk is seen in CMV-seronegative recipients who receive a kidney from a CMV-seropositive donor. These patients are usually given antiviral prophylaxis. Primary disease is the commonest and most severe type of posttransplant CMV infection. This occurs in individuals who have never been infected with CMV who receive an allograft that contains latent virus from a CMV-seropositive donor. The degree of immunosuppression after transplantation. CMV infection occur as a result of immunosuppression Usually seen after four weeks as before this time the immune system has not been fully affected by the immunosuppressants. • Features Interstitial pneumonitis Oesophagitis Peptic ulceration Colitis and Retinitis. • Complications graft rejection renal artery stenosis. • Management Ganciclovir (synthetic guanine derivative) is the most appropriate treatment for CMV concomitant use with ciclosporin leads to elevated creatinine Pancytopenia may occur as

a result of ganciclovir toxicity Foscarnet is the drug of choice for ganciclovir-resistant cytomegalovirus retinitis. the two most common causes of declining renal function post renal transplant are: • graft rejection and • ciclosporin toxicity. Acute pyelonephritis: • high risk of acute episode of pyelonephritis in the transplanted kidney, due to the immunosuppression, the neuropathic bladder and self-catheterisation.

• present like an acute rejection episode, with a tender swollen graft, low-grade pyrexia, and deteriorating graft function. • Especially in the intermediate stage of the post-transplantation immunosuppression, when the patient is most immunocompromised (three to six months post-transplant). Interstitial pneumonia • Cytomegalovirus is the predominant cause of infection in patients within a period of 1-4 months after renal transplantation • A chest X-ray will show a bilateral interstitial or reticulonodular infiltrate that begins in the periphery of the lower lobes and spreads centrally and peripherally BK virus: • C4d staining is used for detection of BK virus after renal transplantation Epstein-Barr virus (EBV) • Epstein-Barr virus (EBV)-associated lymphoproliferative disease (e.g: non-Hodgkin's lymphoma) may occur in individuals with inherited or acquired immunodeficiency syndromes. • Approximately 1% of renal transplant recipients develop post-transplant lymphoproliferative disease (PTLD) in the first year following their transplant. skin cancer • Kidney transplant recipients have a high risk of developing non-melanoma skin cancer, therefore, cancer surveillance is an important consideration in kidney transplant recipients . • The patient may has a malignant melanoma with liver metastases, hence the deranged liver function tests and liver capsule pain. • The patient is often unaware of the melanoma lesion, and the primary lesion may in fact disappear as the disease progresses. Patient may present with RUQ pain and high LFT. • Post-transplant patients are much more prone to develop malignancy compared to normal population. Cyclosporine is one of the main reasons for development of post-transplant malignancy. • Non-melanoma skin cancers (NMSC) are the commonest malignancies in post-transplant state. Of these, squamous cell Ca is the commonest. Kidney donation • Providing there is a sibling who is proven not to have polycystic kidney disease, living related donation should be considered as this would ensure a better match and better graft survival. • Siblings are close genetically, and therefore usually are a better match than spouses. The husband should not be accepted for kidney donation until all siblings have been considered • The age difference is not, however, a contraindication to kidney donation. • Living unrelated kidney donation could also be considered, and is increasing in use in the UK. • Adults should be considered as doner prior to children because renal cysts usually develop during teenage years, so one cannot be confident a child has not been affected until they are at least 20.

Nephrology

Autosomal dominant polycystic kidney disease (ADPKD) Epidemiology • ADPKD is the most common inherited cause of kidney disease, • affecting 1 in 1,000 Caucasians. • Accounting for

approximately 8% of cases of end-stage renal disease (ESRD). • Typically presents between the ages of 30-50. Genetics • Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively • As it is an autosomal dominant, the chance of passing this condition from affected patient to his son is 50%. Types ADPKD type 1 ADPKD type 2 85% of cases 15% of cases Chromosome 16 Chromosome 4 Presents with renal failure earlier, reach ESRF by 50s. Have a slower course, reaching ESRF by 70s. Features • Hypertension (the earliest manifestation of ADPKD) • recurrent UTIs • abdominal pain (loin pain due to a cyst haemorrhage or infection) • renal stones • haematuria (rupture cysts presents with visible haematuria) (Gross haematuria in ADPKD carries a poor prognosis however microscopic haematuria may be a complication) • chronic kidney disease Renal Complications • CKD ADPKD is like a CKD with high phosphate, low calcium but with normal/high Hb due to excess erythropoietin secretion. • Excessive erythropoietin production polycythaemia. • Renal cell carcinoma with lung metastasis: it is very rare but recognized complication of ADPCKD CT Thorax & Abdomen. Extra-renal manifestations • Liver cysts (70%) • Berry aneurysms (8%)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 Subarachnoid haemorrhage may be a cause of mortality in 9% of patients with ADPKD, 8% of patients have an asymptomatic intracranial aneurysm screening for cerebral aneurysms should only be carried out in high risk patients. These include factors such as:

1. Previous rupture of aneurysm
2. Concerning neurological symptoms (for example, severe headache)
3. Positive family history of haemorrhagic stroke or aneurysm. Even if aneurysms are found, the rupture risk can still be low, and the morbidity implications of curative surgery may outweigh conservative management. • Cardiovascular system: mitral valve prolapse (25%) (needs echo screening), mitral/tricuspid incompetence, aortic root dilation, aortic dissection • Colonic diverticula (with any related symptoms, screen by barium enema) • cysts in other organs: pancreas, spleen; very rarely: thyroid, oesophagus, ovary Investigations • Ultrasound (Sensitivity for ADPKD1 is 99% for at-risk patients older than 20 years) Sonographic diagnostic criteria (in patients with positive family history): age < 30 years 2 unilateral or bilateral cysts age 30-59 years 2 cysts in each kidney age > 60 years 4 cysts in each kidney Sensitivity of these criteria nearly 100% for patients 30 years of age or older and for younger patients with PKD1 mutations, 67% for patients with PKD2 mutations younger than 30 years of age. CT scan or MRI should therefore be used in the latter group. one cannot be confident a child has not been affected until they are at least 20: a normal ultrasound scan at 20 years of age means you can be 90% confident they are not affected, a normal scan at 30 increases the confidence level to 98%. Screening is not usually recommended in children because the presence or absence of cysts does not affect management (tight blood pressure control), and the absence of cysts in children does not exclude the disease. All children of affected patients should have their blood pressure monitored at least annually, from early childhood (around age 3) onwards. If cysts are not seen in a younger with a positive family history, the ultrasound should be repeated every five years until the age of 30. • Contrast-enhanced CT scan or MRI Abdominal CT is sensitive for the detection of

cysts however the high radiation dose, particularly in young patients, means it is not widely used as a screening test. should be used if ultrasound is equivocal, especially in patients with PKD2 mutations younger than 30 years of age. CT: More sensitive than USS and may aid in diagnosis in younger patients. MR angiography: In patients with a family history of intracranial aneurysm - to screen for cerebral aneurysms. • Genetic testing The most appropriate strategy to investigate younger with a family history of ADPK is genetic counselling (referral)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology

 The major indication for genetic screening in (ADPKD) is for subjects who are considering donating a kidney to a relative affected by the disease sequence analysis can identify only around 70% of known mutations and linkage analysis requires the availability of sufficient family members. can be used in the following cases: The imaging results are equivocal or inconclusive. To confirm a presumed diagnosis in the absence of family history of the disease (conclusive proof of the diagnosis in these patients relies on mutation analysis). When a definite diagnosis is required in a younger patient, such as a potential living related kidney donor. • Renal biopsy is contraindicated due to a high risk of haemorrhage into a cyst Treatment • high fluid intake (to prevent the formation of renal stones or blood clots) • non-NSAID-based analgesia are the cornerstones of management IV fluids, paracetamol and codeine • Hypertension ACE inhibitors or angiotensin receptor antagonists ACE inhibitors reduce proteinuria and may reduce cyst formation in ADPKD, aliskiren, the direct renin inhibitor, also has early data which show promise with respect to reducing new cysts. • A new therapy (tolvaptan) to delay disease progression (recommended by NICE in 2015) Action: selective vasopressin antagonist inhibit the binding of vasopressin to the V2 receptors reduces cell proliferation, cyst formation and fluid excretion. adverse reactions: thirst, polyuria, nocturia, pollakiuria (frequent urination),↑ liver enzyme. • Urinary tract infections should be treated with lipophillic drugs (for example, ciprofloxacin, trimethoprim-sulphamethoxazole) as they have the best penetration into cyst fluid. • The patient should be offered genetic counselling, despite the fact that the disease has a variable clinical course even between affected family members. • End-stage renal disease → Transplantation Prognosis • the renal function usually deteriorates in a gradual fashion, usually with a drop in creatinine clearance of 5/6 ml/min/year • Approximately half of patients require dialysis by the age of 60 MRCPUK-part-1-January 2016 exam: You are reviewing a patient with adult polycystic kidney disease. Which cardiovascular feature are you most likely to find on examination? Mitral valve prolapse

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Autosomal recessive polycystic kidney disease (ARPKD) • Autosomal recessive polycystic kidney disease (ARPKD) is much less common than autosomal dominant disease (ADPKD). • It is due to a defect in a gene located on chromosome 6 • Diagnosis may be made on prenatal ultrasound or in

early infancy with abdominal masses and renal failure. Newborns may also have features consistent with Potter's syndrome secondary to oligohydramnios. • End-stage renal failure develops in childhood. • Patients also typically have liver involvement, for example portal and interlobular fibrosis. • Renal biopsy typically shows multiple cylindrical lesions at right angles to the cortical surface.

Medullary sponge kidney • is a disorder characterised by dilatation of the collecting ducts in the papillae, with accompanying cystic changes • It is often associated with calculi, which can result in pyelonephritis and renal tract obstruction. • Typically, not inherited but is a congenital condition. The aetiology is uncertain, but it is thought to be a developmental abnormality, possibly resulting from tubular or collecting duct obstruction at any early age. • The kidneys size are normal or increased. • The age of presentation is usually in the third or fourth decade • The majority of cases are sporadic, although a rare autosomal dominant familial form exists with onset in adulthood, and a juvenile autosomal recessive form is also recognised. Recent research has identified a possible defect in the development of the proton pump mechanism in the kidney. • Diagnosis Diagnosis is made via excretion urography, showing small calculi in the papillary zones with surrounding increase density; this is because the dilated collecting ducts are filled with contrast medium About 20% of patients have associated hypercalciuria or renal tubular acidosis Skeletal hemihypertrophy may be associated Renal failure is highly unusual

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Alport's syndrome • Alport syndrome is the second most common inherited cause of renal failure (after polycystic kidney disease) • usually inherited in an X-linked dominant pattern. Inheritance is variable, but the majority are X linked dominant (85%) ; Therefore, as only the Y chromosome is passed from father to son there is no chance of the son having the disease.

Nephrology

 15% are autosomal recessive with rare autosomal dominant variants • Most cases arise from the COL4A5 gene on the X chromosome . • It is due to a defect in the gene which codes for type IV collagen resulting in an abnormal glomerular-basement membrane (GBM). Patients with Alport syndrome are at risk of developing antiglomerular basement membrane disease (Goodpasture's disease) following transplantation, as their immune systems have never been exposed to type IV collagen and hence lack tolerance. What is the most likely reason for the decline in graft function? Anti-glomerular-basement membrane antibodies (Goodpasture's syndrome) • There is a high spontaneous mutation rate, which means 20% of patients have no family history. • Prevalence is around 1 in 5000 • The disease is more severe in males with females rarely developing renal failure • usually presents in childhood. • more severe in males females do not develop progressive renal failure with this condition. • A favourite question is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies leading to a Goodpasture's syndrome like picture Features "Can't see, can't pee, can't hear a bee." • microscopic haematuria Most common and earliest manifestation • progressive renal failure • bilateral sensorineural deafness (usually occurs before the onset of renal failure) • ocular

Anterior lenticonus protrusion of the lens surface into the anterior chamber Occurs in 25% of patients is the pathognomonic feature of Alport syndrome Dot-and-fleck retinopathy Most common ocular manifestation of patients with Alport syndrome, (occurring in 85%) retinitis pigmentosa Investigations • renal biopsy: Light microscopy usually unremarkable and electron microscopy is usually required. Electron microscopy splitting of lamina densa basket weave pattern of glomerular basement membrane foam cells produced by lipid accumulation in visceral epithelial cells • slit lamp examination: bilateral thin lens capsules conical protrusions on the anterior aspect of the lens, subcapsular cataracts.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Treatment • Rigorous control of hypertension may delay the onset of end stage renal failure, • angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers if they have proteinuria • Renal transplant Prognosis • ESRF seen in 90% of patients with Alport's by the age of 40 years. MRCPUK-part-1-September 2009 exam: What is the mode of inheritance of Alport's syndrome in the majority of cases? X-linked dominant MRCPUK-part-1-January 2008 exam: Alport's syndrome is due to a defect in:? Type IV collagen

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Haemolytic uraemic syndrome The presence of thrombocytopenia and evidence of haemolysis in association with bloody diarrhoea should make you think of haemolytic uraemic syndrome (HUS). Haemolytic uraemic syndrome is generally seen in young children and produces a triad of: • acute renal failure • microangiopathic haemolytic anaemia • thrombocytopenia with normal clotting. Causes • post-dysentery - classically E coli 0157:H7 ('verotoxigenic', 'enterohaemorrhagic') .Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs. Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion. The syndrome has also been reported after infections with coxsackie, echovirus and Shigella. • tumours • pregnancy • ciclosporin, the Pill • systemic lupus erythematosus • HIV • Inherited recurrent HUS has been described with both dominant and recessive patterns of inheritance Investigations • full blood count: anaemia, ↓↓Serum haptoglobins (which bind haemoglobin), thrombocytopaenia, fragmented blood film The hallmark of HUS is the appearance of schistocytes (fragmented, deformed, irregular, or helmet shaped red cells) on the blood film. • There is normal coagulation and fibrinogen. • U&E: acute renal failure • stool culture

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology Major differential diagnosis is:

1. Sepsis with DIC - presents with abnormalities of clotting parameters.
2. TTP - thrombotic thrombocytopenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease. Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS. Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of

central nervous system involvement in TTP and the more severe renal involvement in HUS. In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common. feature HUS TTP Acute kidney injury more severe Less severe Neurological symptoms less common More common Complications include: • Stroke, seizure and coma occur in 25% of patients • Rarely pancreatitis, and • Pleural and pericardial effusions. • Approximately 5% of patients will develop end stage renal failure. Management • treatment is supportive e.g. Fluids, blood transfusion and dialysis if required • there is no role for antibiotics, despite the preceding diarrhoeal illness in many patients • the indications for plasma exchange in HUS are complicated. As a general rule plasma exchange is reserved for severe cases of HUS not associated with diarrhoea • Non-steroidal anti-inflammatory drugs and anti-diarrhoeals should be avoided Prognosis • Most children recover spontaneously from the illness, but mortality may be high in the elderly. • Unfortunately fatality rates from HUS remain high, at between 5 and 10%. MRCPUK-part-1- September 2012 exam: H/O bloody diarrhea and dehydration + ↓Platelet , ↑WBC, ↑urea & creatinine. Given the likely diagnosis, which organism is the most likely cause? E. coli MRCPUK- part-1- May 2010 exam: Feature of diarrhoea , lethargy & acute renal failure. There is a known local outbreak of E coli 0157:H7. Given the likely diagnosis, which one of the following investigation results would be expected? Fragmented red blood cells (Δ haemolytic uraemic syndrome)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Renal tubular defects • thick ascending limb of Henle's loop: Bartter syndromes are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride in the thick ascending limb of Henle's loop • distal convoluted tubule: Gitelman syndrome are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride due to defect of thiazide-sensitive Na-CI cotransporter in the distal convoluted tubule • proximal tubule: Carbonic anhydrase is expressed in the proximal tubule and is inhibited by acetazolamide; this is manifested biochemically by normal anion-gap metabolic acidosis Fanconi syndrome refers to a proximal tubular defect that results in wasting of phosphate, calcium and amino acids . seen in: cystinosis myeloma kidney Wilson's disease • collecting ducts : Aquaporin channels are expressed in the cortical collecting ducts and are involved in water handling; defects result in diabetes insipidus You may find it useful to remember the location of the nephron defects in these conditions as being alphabetical, i.e. Bartter affects the thick ascending limb, Gitelman affects distal tubule and Liddle syndrome affects the collecting ducts. BGL is in alphabetical order, as is the order of the affected location in the nephrons.

Fanconi syndrome Pathophysiology • Autosomal recessive • Generalised dysfunction of the proximal tubule, with the resultant urinary loss of bicarbonate, calcium, phosphate, urate, amino acids, glucose, and other organic acids and bases. • The proximal convoluted tubule cells are unable to reabsorb HCO3- leading to increased HCO3- excretion in the urine →Type 2 (proximal) renal tubular acidosis (RTA) Causes • Inherited disorders Cystinosis (most common cause in children) Wilson's disease Type 1 glycogen storage disease • Sjogren's syndrome • Multiple

myeloma • Nephrotic syndrome • Drugs: e.g. Rifampicin , Expired tetracycline antibiotics, aminoglycosides • Heavy metal poisoning (e.g., lead, cadmium, mercury) • Ischemia (acute tubular necrosis) • Amyloidosis • Vitamin D deficiency • Paroxysmal nocturnal haemoglobinuria

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology Feature • Polyuria, aminoaciduria, Glucosuria despite normal or low serum glucose • Phosphaturia → Hypophosphatemia • Hypouricemia • In children → growth retardation, renal rickets • Metabolic acidosis • Osteomalacia Treatment • Replacement of lost electrolytes including potassium, phosphate, bicarbonate. • Treatment of the cause Fanconi syndrome • Renal proximal convoluted tubular dysfunction. • Symptoms: Failure to thrive (poor growth), hypokalaemia (muscle weakness or spasms, fatigue, palpitations), and hypophosphatemia (rickets, abnormal growth).

Bartter and Gitelman syndromes Definition • Bartter and Gitelman syndromes are an autosomal recessive renal tubular defects result in hypokalemic salt-losing (ie, salt-wasting). Pathophysiology • Gitelman syndrome: a loss of function mutation defect in thiazide-sensitive Na-CI cotransporter in the distal convoluted tubule • Bartter syndrome: a loss of function mutation defect in sodium chloride reabsorption in the thick ascending limb of Henle's loop (NKCC2) • Hypokalemia, hypochloraemic metabolic alkalosis, polyuria, low to normal blood pressure, all result from impaired sodium chloride reabsorption. • Renal biopsy →Hyperplasia of the juxtaglomerular apparatus is characteristic Similar features (both Bartter and Gitelman) • Often asymptomatic • fatigue, cramps and weakness. • Salt craving, thirst, polydipsia, polyuria and nocturia. • Normotensive hypokalaemic metabolic alkalosis • ↑sodium loss in the urine →volume depletion, → ↑serum renin and aldosterone → potassium loss in the urine Different features (which may differentiate Bartter from Gitelman) • Gitelman: most common, present in adolescence and early adulthood, has milder symptoms, pseudogout hypocalciuria severe hypomagnesemia. • Bartter: present in children or early adolescence, has more severe symptoms, sensorineural deafness

 hypercalciuria and normal or mild hypomagnesemia. increased prostaglandin E2 (PGE2) production Diagnosis approach • Step 1: suspicion: Bartter or Gitelman syndrome should be suspected in any patient with unexplained hypokalemia, metabolic alkalosis, and a normal or low blood pressure. • Step 2 : exclude other more common causes of these findings, in particular diuretic and/or laxative abuse and surreptitious vomiting → Urine diuretic screen. • Step 3: spot urine chloride (repeated several times) consistently high (>20 mEq/L) in Bartter and Gitelman syndromes. consistently low (<20 mEq/L) with vomiting fluctuates between low and high with intermittent (and surreptitious or denied) diuretic use (high when the diuretic effect is present and low when it dissipates). • Step 4: genetic testing Distinguishing Bartter syndrome from Gitelman syndrome Bartter syndrome Gitelman syndrome SLC12A1 (Bartter syndrome type I) SLC12A3 Gene affected 1 in a million. 1 in 40,000 prevalence Thiazide-sensitive Na-CI cotransporter in the distal convoluted tubule Site of defect present in adolescence and early adulthood Presentation) milder symptoms (Concentrating capacity reduced and diluting capacity reduced Concentrating capacity normal/near normal and diluting capacity reduced Concentrating and diluting abilities Increased

(hypercalciuria) Reduced (hypocalciuria) Urinary calcium either normal or mildly reduced severe hypomagnesemia is common Serum magnesium Treatment (for Bartter or Gitelman syndrome) • First line: Electrolyte supplementation (sodium, potassium, and magnesium salts) • Second line: Potassium-sparing diuretics that inhibits distal sodium-potassium exchange, such as spironolactone, eplerenone, or amiloride. • Third-line: NSAIDs or ACE inhibitors Notes & Notes for MRCP
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Sodium chloride reabsorption in the thick ascending limb of Henle's loop (NKCC2) Most cases are discovered in infancy or early adolescence (more severe symptoms)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology

Locations of renal tubular defects SAME: Syndrome of Apparent Mineralocorticoid Excess The effects of Gitelman syndrome are similar to those of a thiazide diuretic. The effects of Bartter syndrome are similar to those of a loop diuretic. Loop diuretics work by inhibiting NKCC2- Think of Barters syndrome as like taking large dose of furosemide. Gitelman's syndrome: Normotensive hypokalaemic metabolic alkalosis with Hypocalciuria and significant hypomagnesaemia. The hypokalemia with normal blood pressure in a middle aged male without any skeletal abnormalities or retardation would suggest a diagnosis of Gitelman syndrome rather than Bartter’s syndrome. Bartter syndrome: Normotensive hypokalaemic metabolic alkalosis with hypercalciuria, normal or mild hypomagnesaemia, metabolic alkalosis.

Renal tubular defects Causes Defect Effect Note Bartter syndrome Autosomal recessive Reabsorption defect in thick ascending loop of Henle (affects Na+ /K+/2 Cl – cotransporter) Gitelman syndrome Autosomal recessive Reabsorption defect of NaCl in distal convoluted tubule Liddle syndrome Autosomal dominant Gain of function mutation →□ Na+ channel degradation → ↑Na+ reabsorption in collecting tubules Fanconi syndrome Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drug s (eg, cisplatin), lead poisoning Generalized reabsorption defect in PCT excretion of amino acids , glucose, HCO3 –, and PO43 –, and all substances reabsorbed by the PCT Syndrome of Apparent Mineralocortid Excess (SAME) Autosomal recessive OR acquired from glycyrrhetinic acid (present in liquorice), which blocks activity of 11β-hydroxy steroid dehydrogenase Cortisol activates mineralocorticoid receptors;11β-HSD converts cortisol to cortisone (inactive on these receptors) Hereditary 11βHSD deficiency →↑cortisol →↑mineralocorticoi d receptor activity Notes & Notes for MRCP
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Normotensive hypokalaemic metabolic alkalosis hypercalciuria Presents similarly to chronic loop diuretic use Normotensive hypokalaemic metabolic alkalosis, hypomagnese mia, hypocalciuria Presents similarly to life-long thiazide diuretic use Less severe than Bartter syndrome Hypertensive hypokalaemic metabolic alkalosis, ↓aldosterone Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable. Treatment: amiloride Hypokalemic metabolic acidosis (proximal

RTA), hypophosphat emia Growth retardation and rickets/ osteopenia common due to hypophosphatemia Volume depletion also common Hypertensive hypokalaemic metabolic alkalosis, ↓aldosterone, Cortisol tries to be the SAME as aldosterone Treatment: K+- sparing diuretics (↓mineralocorticoid effects) or corticosteroids (exogenous corticosteroid →↓ endogenous cortisol production →↓ mineralocorticoid receptor activation)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology

Liddle's syndrome Pathophysiology • Autosomal dominant (gain of function mutation) → ↑activity of Epithelial Sodium Channels (ENaC) → ↑reuptake of water and sodium → activation of sodium/potassium exchange independent of circulating mineralocorticoid (pseudohyperaldosteronism). Diagnostic features • Hypertension • Hypokalaemia • Metabolic alkalosis • Decreased renin and aldosterone levels Treatment • Amiloride: Potassium-sparing diuretics: acts directly on the sodium channel → (epithelial sodium channel (ENaC) antagonists) • Spironolactone is not an effective treatment as the increased activity of the ENaC is not mediated by aldosterone. Top Tips hypokalaemic alkalosis + suppressed renin and aldosterone + hypertension →Liddle’s syndrome The clinical features of Liddle syndrome are similar to those of hyperaldosteronism, except that Liddle syndrome manifests with decreased renin and aldosterone levels.

Glomerulonephritides Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis: Membranous glomerulonephritis • presentation: proteinuria / nephrotic syndrome / chronic kidney disease • cause: infections, rheumatoid drugs, malignancy • 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop chronic kidney disease IgA nephropathy - aka Berger's disease, mesangioproliferative GN • typically young adult with haematuria following an URTI Diffuse proliferative glomerulonephritis (DPGN)