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Chronic Glomerulonephritis

BEWARE! Asymptomatic hematuria can mean ANY DAMN THING.
Glomerulonephritis is JUST ONE POSSIBILITY.
BUT!... if there is also PROTEINURIA, you must keep GN in the back of your mind.

IgA Nephropathy is the commonest GN cause of asymptomatic hematuria

Commonest among young males, 2nd to 3rd decades of life.

PRESENTATION and NATURAL HISTORY

- In 50-60% of cases **ASYMPTOMATIC GROSS HEMATURIA**
- In 30% of cases, **ASYMPTOMATIC MICROSCOPIC HEMATURIA**
- In 10% of cases, **NEPHROTIC SYNDROME or ACUTE GLOMERULONEPHRITIS**
- **Simultaneous Respiratory or GIT infection**
- 10-20 years later, **END STAGE RENAL FAILURE** . Especially if:
  - elderly
  - male
  - hypertensive
  - proteinuric
  - already crappy kidneys

AT-RISK GROUP!! Should at least ATTEMPT TO RETARD PROGRESSION TO END STAGE RENAL FAILURE

SO WHAT DO I DO?

Supportive management.

- Keep fluid balance in the realms of normality
- Diuretics for overload, saline for dehydration.
- If your patient runs the risk of progressing to ESRF, try corticosteroids or fish oil.
- **ACE inhibitors for all!**
- Ang II receptor blockers for some.

So many trials, so many mixed results:

- **Corticosteroids:** decrease proteinuria, but no change in disease progression. Pfft.
- **Fish Oil**: n-3 fatty acids should limit the production and/or action of cytokines at the glomerulus. Some success. One very wonky trial showed extreme benefit. 6% fish-oilers doubled their serum creatinine over 4 yrs , versus 33% of placebo group.
- **ACE inhibitors**: there is OBVIOUS BENEFIT; **All experts agree**.

THEREFORE:

- **FBC** anaemia is a sign of chronicity.
- **EUC** mainly interested in creatinine
- **BSL** maybe diabetic nephropathy
- **Coags** maybe coagulopathic if nephrotic
- **ECG** dehydration, hyperkalemia- probably dangerous…
- **Urinalysis + microscopy** -dysmorphic RBCs? = Glomerulonephritis
- **24hr urinary protein -** ? nephrotic range?.
- **IgA titres** should be elevated in IgA nephropathy
- **ANA, ASOT**
- **C3, C4 complement**

LUPUS: active SLE will have a low C3 / C4 due to complement depletion;

But then… BIOPSY and

- Light Microscopy
- Electron Microscopy
- Immunofluorescence

Accurate histological diagnosis

Acute Glomerulonephritis

- **Abrupt onset of obvious macroscopic hematuria**
- **Oliguria**
- **Sudden decrease in glomerular filtration rate →**
- **Proteinuria below nephrotic range (<3g/day)**
- **OEDEMA occuring as a result of sodium retention and not hypoalbuminaemia**

ITS ALMOST ALWAYS A POST-INFECTIOUS SITUATION!

Triggering Events:

- **POST-INFECTIOUS eg. post-streptococcal**
  - **Mainly in young children with a runny nose**
  - **Occurs ~2weeks after the initial infection**
  - **Mediated by immune-complex deposition AND by the accumulation of streptococcal antigens in the glomerular filtration membrane... which then attract all kinds of immune retribution, mainly in the shape of angry complement and macrophages.**

Creatinine: measure of GFR

released from skeletal muscle at a steady rate; high level is associated with large muscle mass and exercise

high creatinine better be found in a large well-muscled patient, not a frail 90 yr old woman.

THUS in a hypovolemic patient the GFR will drop and thus the serum creatinine will RISE

Normal creatinine = GFR must be OK

FILTRATION RATE: ~100 ml per minute; = Carefully controlled!

Very steady between 90 and 200 systolic

only extremes of blood pressure influence the GFR.

INCREASED BP = reflex contraction of smooth muscle in afferent arteriole, thus reduced flow still means GFR maintained at the same level

Natural History

RESOLVES SPONTANEOUSLY! No cause for dismay

Strep infection;

- **1-2 weeks later: onset of oedema + hemoproteinuria**
- **1-2 weeks of oedeme and hemoproteunuria with massively elevated creatinine and Na+**
- **1-2 weeks of wild diuresis**
- **1-2 weeks of continuing creatinine abnormalities, tapering off;**
- **6 months of hematuria**
- **X years of proteinuria (variable; persists for 10 years in 2% of patients)**

Only 1 or 2% of post-strep GN patients progress to ESRF

Diagnostic Side-Dishes

BIOPSY with immunofluorescence and electron microscopy is the *ONLY MEANS OF DIAGNOSIS...*

and you may not want to biopsy the kidneys of that chubby 5 year old boy

Certain immunological changes take place in post-infectious GN, and these can be employed to point the way towards a diagnosis.

COMPLEMENT components, esp. C3 are depressed during the early course.
THESE SHOULD RETURN TO NORMAL 6-8 weeks after onset
IF THEY HAVE NOT: !! RED FLAG !! it may be lupus nephritis

STREP ANTIBODIES wont diagnose post-strep GN for you, but they will tell you if a strep infection has taken place recently.
...Look for antibodies to...

- **Streptolysin O** (be warned- only 66%of streptococci wield this weapon)
- **Streptokinase**
- **Hyalouronidase**
- **Nicotinamide Dinucleotidase**

MANAGEMENT IS SUPPORTIVE and consists of....

MANAGING FLUID OVERLOAD with diuretics

MANAGING HYPERTENSION which results from fluid overload with conventional agents

The NEPHROTIC SYNDROME

Leakage of 3 grams of protein per day.

Pathophysiology

You have a charge barrier and a size barrier. Normally nothing larger than 70kD and nothing polyanionic can get through. With GBM damage, both of these barriers can be disrupted.

SEQUELAE and STRATEGIES FOR THE MANAGEMENT THEREOF

Oedema: due to protein loss uncompensated by liver synthesis and tissue mobilsation of albumin

Sodium Retention: due to increased distal resorption; ? due to activated RAAS?

Loop

Must get rid of the extra sodium. Loop diuretics and salt restriction are the go. Might even want to combine frusemide with a thiazide or a K-sparing diuretic. NOTE: frusemide has a short half life. Use it 2-3 times a day in large doses. BEWARE: abrupt natriuresis can cause a sudden hypovolemia and even ARF! Plus by excreting so much water you will hyperconcentrate the blood, so give these diuretics in tandem with heparin and TED stockings.

Thromboembolic Complications: especially renal vein thrombosis! This is due to a number of factors, only one of which is the increased excretion of anticoagulation proteins (eg. antithrombin III) into the urine. There is aso unexplainable thrombocytosis (? Due to hyperconcentration of blood cells? Remember, all that water moving out into the interstitial spaces leaves behind the cells in the blood.);

Heparin

Aspirin

Must prevent thromboembolism. Just give them heparin, evidence shows that the number of fatal emboli prevented is greater than the number of fatal bleeding events induced. Also consider aspirin (because much of the antithrombin III has been excreted and heparin has fewer targets to bind with).

Infectious Complications: you are peeing out all of your immunoglobulins and complement cascade components. Especially dangerous in children.

Sadly, still no justification for prophylactic antibiotics, as you may end up simply selecting for resistant organisms. Use ad-hoc intravenous antibiotics.

Hyperlipidaemia: due to overproduction and under-catabolism of LDLs. Undercatabolism seems to result from urinary excretion of ..something. Something vital to lipid catabolism. Exactly what it is has not been determined yet. Nor do we know what causes the increased synthesis of blood lipids.

Low-fat Diet
Statins
ACE-inhibitors

Manage this with a soy-based low fat diet and statins. ACE-inhibitors also help indirectly, by reducting protein excretion.

ACE Inhibition: indicated even in normotensive patients. The BP-lowering effects take place within 24hrs, but the antinephrotic protein-saving effects take a month. The anti-nephrotic effect is totally unrelated to the blood-pressure effects, its a completely different poorly understood mechanism. It can be enhanced with a low-sodium diet and diuretics.

Common Causes

- **Diabetic Nephropathy**
- **Minimal Change Glomerulopathy (idiopathic)**
  - Loss of charge selectivity
- **Membranous glomerulonephritis (often linked to neoplasia)**
  - Carcinomas, lymphoma, leukaemia, myeloma, sarcoma...
  - Loss of size selectivity
- **Primary Renal Amyloidosis**
- **HIV**
- **Preeclampsia**

Chronic Glomerulonephritis

PROGRESSIVE loss of renal function associated with inflammation.
CREEPS UP ON YOU: most commonly an incidental finding, for example:

- Routine Urinalysis:
  - Proteinuria and hematuria
- Routine FBC:
  - Normocytic normochromic anaemia
- Abdominal Imaging:
  - Bilateral small kidneys

Usually a chronic GN results from the resolution of an acute GN. Initial injury = reduction in the number of working nephrons. Therefore your GFR aint what it used to be, and the remaining nephron units detect this and hypertrophy to compensate.
So now you are working your few remaining nephrons much harder: the same amount of blood needs to get filtered, but the filter is much smaller and thus the blood is forced through it at a greater pressure. This is fine for a while, but we all know what happens to arterioles under constant hemodynamic stress: SCLEROSIS. Thats right, the glomeruli literally work themselves into an early grave. Hence the progression to end-stage renal failure (ESRF)

DISEASE DEFINITIONS: "STAGING"

- **Stage 1:** kidney damage with a normal GFR (≥90 mL/min). The action plan is diagnosis and treatment, treatment of comorbid conditions, slowing of the progressing of kidney disease, and reduction of cardiovascular disease risks.
- **Stage 2:** kidney damage with a mild decrease in the GFR (60-90 mL/min). The action plan is estimation of the progression of kidney disease.
- **Stage 3:** moderately decreased GFR (30-59 mL/min). The action plan is evaluation and treatment of complications.
- **Stage 4:** severe decrease in the GFR (15-29 mL/min). The action plan is preparation for renal replacement therapy.
- **Stage 5:** kidney failure. The action plan is kidney replacement if the patient is uremic.

General approach:

Find and treat the systemic cause.
No apparent cause?
→ TREAT UREMIA
→ DELAY END-STAGE RENAL FAILURE
→ DIALYSIS
→ TRANSPLANTATION

MONITORING PROGRESSION:

URINALYSIS: to calculate protein loss using protein / creatinine ratio
Eg. 300 protein and 150 creat. = 300 / 150 = 2 (g protein/day)
EUC: to calculate GFR using online creatinine clearance calculator in CIAP
Use this to monitor response to therapy; GFR = all important
ALSO look at calcium (low?), phosphate (high?)
FBC looking for normochromic normocytic anaemia
Albumin: to monitor effect of protein loss
COAGS: watch out for thrombophilia
..may also want to do a kidney ultrasound:
? TINY SHRUNKEN KIDNEYS = DONT BOTHER WITH THE BIOPSY
all end stage renal disease looks the same under the microscope (i.e. scar tissue)

Usually secondary to
Another glomerulopathy, gone chronic;
Rare hereditary stuff, eg.

- **Alport syndrome:** Mutation in type IV collagen, = GBM is 5 times thicker
- **Sickle cell anaemia:** Due to sustained glomerular hypertension
- **Fabry Disease:** Lysosomal storage disease, X-linked mutation in the a-galactosidase gene, causing small vessel dysfunction at the kidney and elsewhere
- **Plus Lypodystrophy, "Nail-Patella" syndrome, etc etc**

Connective tissue diseases

- **Amyloidosis** with Rheumatoid Arthritis
- **Lupus Nephritis**

Infection

- **Hepatitis B and C**
- **HIV**
- **Secondary to infective endocarditis**
- **P. falciparum malaria**

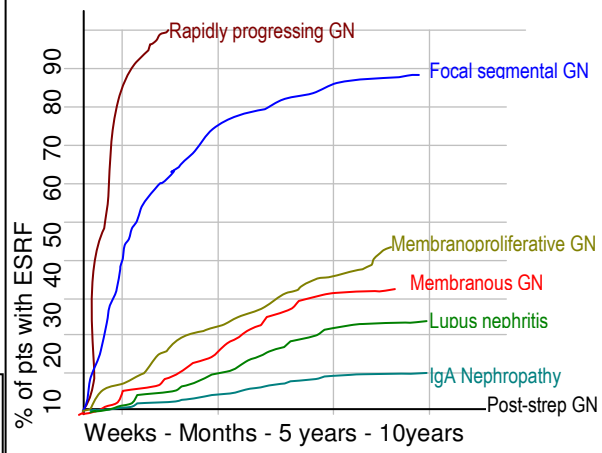
Neoplasia

- **Hodgkins' Lymphoma**

Drugs

- **NSAIDs**
- **Gold therapy**
- **Penicillamine**
- **IV heroin**

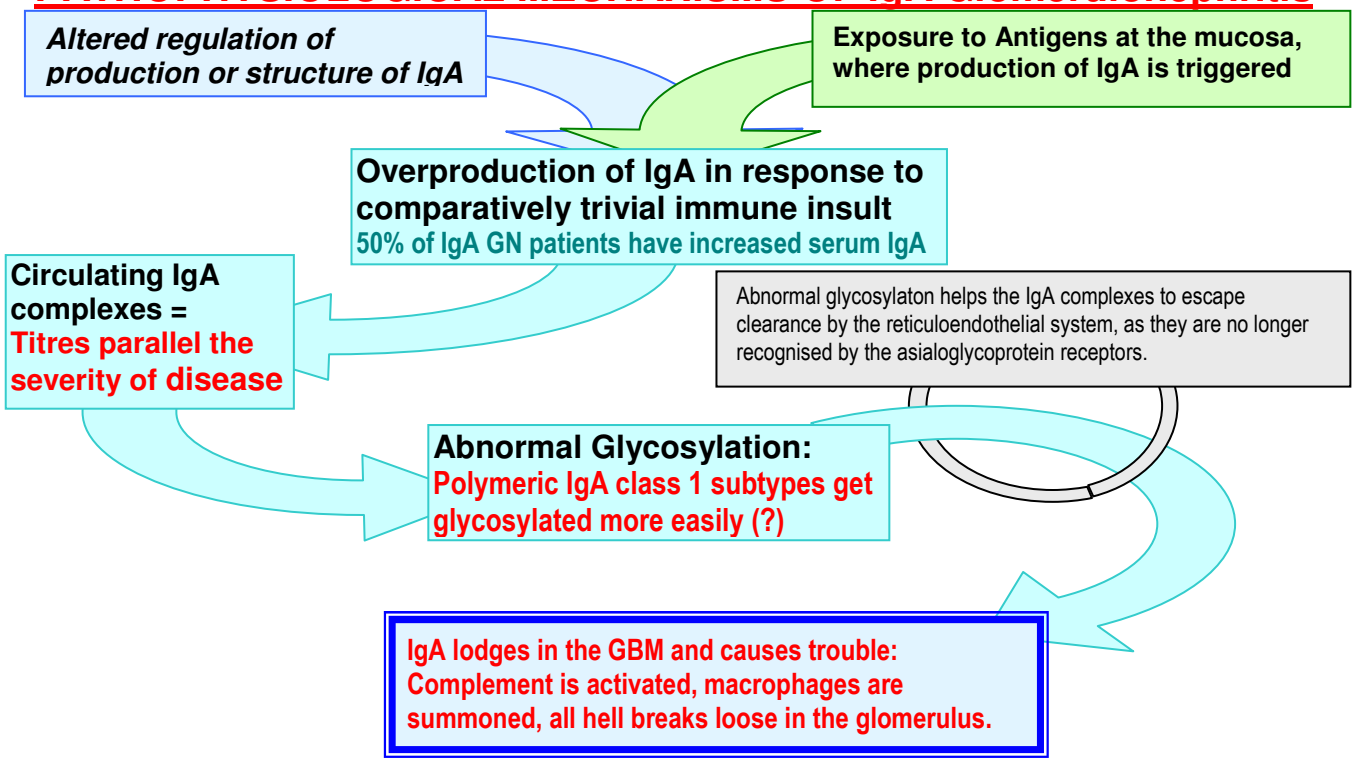
Rates of Progression to ESRF



GOALS OF MANAGEMENT:

- **Reduce blood pressure (ACE-I, lasix, etc)**
- **Replace EPO and activated Vitamin D**
- **Manage hyperlipidaemia (reduce CVS risk factors)**
- **Give heparin if pro-thrombotic**
- **Discuss transplant + Dialysis**

PATHOPHYSIOLOGICAL MECHANISMS OF IgA Glomerulonephritis



Rapidly Progresive Glomerulonephritis

Just like acute glomerulonephritis, but in fast forward: rapid decline in renal function , and subsequent end-stage renal failure within days or weeks.
LUCKILY ITS RARE. 2 to 4% of GN are rapidly progressive.

PATHOLOGICAL HALLMARKS:
Cellular crescents surounding the glomeruli.
- these are made of endothelial cells, mononuclear infiltrate and recruited fibroblasts.

ALSO:
- linear deposition of immunoglobulins all along the GBM in 20%
- granular (blobby) deposition of these Ig's in the GBM in 30%.
- In the remainder of pts, no immune deposits of any sort are detectable.

Natural History

- **INSIDIOUS ONSET:**
  - **Malaise, lethargy, microscopic hematuria**
  - **Proteinuria in ~30% of patients**
- **KNOW TO LOOK FOR RARE DISEASES KNOWN TO BE ASSOCIATED WITH RAPIDLY PROGRESIVE GN:**
  - **a VASCULITIS of some sort, be it**
    - **WEGENER'S GRANULOMATOSIS,**
    - **MICROSCOPIC POLYANGIITIS, or**
    - **CHURG-STRAUSS SYNDROME**
  - **CRYOGLOBULINAEMIA**
  - **SYSTEMIC LUPUS ERYTHEMATOSUS**
  - **GLOMERULAR BASEMENT MEMBRANE ANTIBODIES**
  - **GOODPASTURE'S SYNDROME (also haemoptysis)**

MANAGEMENT is AGGRESSIVE and DETERMINED.

Kick-start with **IV corticosteroids and cyclophosphamide**
Monitor progress: if response is limited move on to **PLASMA EXCHANGE**
(thats if you can identify an antibody as the culprit)

Renal survival is most closely related to serum creatinine titres at presentation.
Only 40% of patients escape dialysis at 1 year of follow-up.