AGN & Nephrotic Syndrome

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ACUTE GLOMERULONEPHRITIS

(ACUTE NEPHRITIC SYNDROME)
A 6-year-old boy presents with coke-colored urine. His mother reports that he had a sore throat 8 days prior to presentation. On physical exam, looks pale, blood pressure is 136/88 mm Hg, and he has mild swelling of the face and lower extremities. Of the following, the MOST likely laboratory finding is:

- A. low C3 complement value
- B. normal urinalysis results
- C. positive antineutrophil cytoplasmic antibody titer
- D. positive antinuclear antibody titer
- E. positive urine culture
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The triad haematuria, edema and oliguria
Definition

- Glomerulonephritis refers to a specific renal dx xterized by inflammation and proliferation of cells within the glomerulus.

- To the clinician acute is temporally related, meaning a sudden onset and to the pathologist, acute indicates the histologic finding of polymorphonuclear leukocytes in the glomeruli.
• AGN is characterized by sudden often explosive onset of symptoms of glomerular injury, which includes:
  - Haematuria-grossly (40%) evidenced by coke-coloured urine or microscopic (60%)
  - Hypertension-? Na\(^+\) + H\(_2\)O retention (70%).
  - Oedema – seldom as marked as in nephrotic syndrome (90%)
  - Oliguria – urine volume <300mls/m\(^2\), amount required for excretion of minimal solute load. (33%)
  - Circulatory congestion – pulmonary oedema and heart failure
  - And a varying degree of renal insufficiency
Other findings include:

• Proteinuria – modest elevation of 30-100mg/dl (90%)

• Active urinary sediment

• Findings consequent upon ↓ GFR:
  a. azotaemia –(Normal range of urea =15-45mg/dl)
  b. ↑ creatinine (Normal range = 0.5 - 1.2mg/dl)
  c. Hyperphosphataemia
  d. Hyperuricaemia
  e. ± hypocalcaemia (due to hyperphosphataemia)
Acute Nephritic Syndrome in children

**Common**
- Post infectious GN
- HSP

**Less common**
- MPGN
- IgA Nephropathy
- SLE
- Infective Endocarditis –related
- Shunt nephritis

**Uncommon**
- Wegener’s granulomatosis
- Polyarteritis nodosa
POST-STREPTOCOCCAL AGN

- The prototype of AGN

- 1st noticed agent is Lancefield group A B-haemolytic streptococcus

- Pharyngeal or cutaneous infection (pyoderma, scabies) by the organism are the common antecedents.

- Nephritogenic strains of Streptococcus – serotypes in pharyngitis - associated AGN are : M type 12 frequently), 1, 4, 6, 25 (occasionally)

- In pyoderma-related – AGN : M type 49 + others 53, 55, 56, 57, 58.

- NB: There are Rheumatogenic strains of the Streptococcus
EPIDEMIOLOGY

• Features of post streptococcal AGN vary from mild to severe

• Mild cases usually evade detection therefore incidence difficult to determine (4:5)

• M > f = 2:1

• Commonly seen in early school age; peak 6-7 years
• Strept. pharyngitis occurs primarily b/w the ages of 5-15, most commonly in winter and spring.

• **20% of asymptomatic** school children are carriers; thus AGN may be seen without a prior symptomatic pharyngitis.

• Treatment of the pharyngitis does not prevent AGN; may decrease spread of nephritogenic strains.
• Impetigo is more common in summer and fall.

• **Pts tend to be younger than those with pharyngitis.**

• The overall attack rate of APSGN in the presence of a nephritogenic strain is 15% regardless of site of infection.

• 50-85% of cases of APSGN may be asymptomatic,

• <1% develop RPGN.

• In our environment, pyoderma-related APSGN appears more common.
Pathogenesis

• Not well understood

• Deposition of preformed immune complexes in glomerular structures or fixation of complement and antibody with antigen in glomerular bed

• Cytokines and oxygen radicals released in the inflammatory process appear to decrease glomerular blood flow and change the basement membrane permeability
Pathophysiology

• Inflammation and changes in the BM permeability result in decreased GFR.

• Decreased GFR leads to fluid retention, HTN and oedema.

• If solute filtration is greatly reduced, may result in azotaemia with acidosis hyperkalaemia and hyperphosphataemia.
Acute post-infectious glomerulonephritis
CLINICAL FEATURES

Typical picture is infection of the skin or the pharynx; followed by a latent period of about 10/7(1-3wks) for pharyngitis associated AGN and 3-6wks for pyoderma associated AGN before appearance of features of AGN:

A. Oedema – milder than in Nephrotic syndrome
   Facial, limbs, worse on waking up,
   disappears later in the day/with ambulation

B. Hypertension – which falls with recovery
C. Haematuria – gross in 30-70% of pts.
   (Brownish, coca-cola, tea or agbo coloured due→ to degradation of Hb to acid heamatin)
   Microscopic haematuria in all

D. Signs of circulatory overload
   - Pulm oedema →resp. distress, crepts
   - Heart failure →tachycardia, tachypnoea, gallop rhythm, tender hepatomegaly

E. Severe pallor → dilutional anaemia

F. Evidence of pharyngitis or pyodema. Siblings may have evidence of AGN.
Severe cases – present with complications of the dx.

1. Hypertensive encephalopathy - Convulsions, impaired consciousness, paresis.

2. Oliguric acute renal failure

3. Pulmonary oedema

4. Heart failure

5. Nephrotic syndrome
   - Massive oedema + proteinuria
   - A rare cause of Nephrotic syndrome in our environment

6. Retinopathies

7. RPGN → renal failure
Evaluation to Document Likelihood of Typical Poststreptococcal Acute Glomerulonephritis

- Typical presentation with no findings suggestive of other systemic disease.

- Evidence of prior streptococcal infection.
  - Throat or skin lesion culture positive for Streptococci
  - Elevated antibody titers using panel (acute and convalescent titers must be done)

- Complement abnormalities typical
  - Decreased CH50 and C3 during acute phase.
  - C4 usually normal
  - Levels rise toward normal by 6-8 weeks
• Beginning recovery in 1 week
  – Diuresis
  – Blood pressure normalizes
  – BUN, creatinine begin to fall.

• Normalization of urine sediment
  – Resolution of gross hematuria by 2-3 weeks
  – Resolution of proteinuria by 3-6 months
  – Resolution of microscopic hematuria by 1 year
Investigations contd.

- Urinalysis – (part of the examinations in the side room)
- Colour, blood, protein (+ or ++),

-Microscopy → rbc ++++, wbc casts – esp rbc casts.

{Casts are proteins filtered but not reabsorbed which form moulds at the tubules, rbcs attached - Rbc casts
  Granular casts etc (when rbc degenerate), Hyaline casts.}
• Serum electrolyte
  - Na
  - Cl = (N)
  - ↑K+
  - ↓HCO$_3^-$
  - ↑Urea, ↑creatinine
- Serum protein- (N)
• Serum C3 estimation
  - Complement system is activated in post streptococcal AGN
  - Serum C3 is decreased for 6-8/52 before returning to normal; Serum C4, (N)
  - If not normal by 8-12 wks, review diagnosis.
• Serum cholesterol- to R/o N. syndrome
• 24hour urine for protein and creatinine clearance
• Blood film for mp
• Chest X-ray-if heart failure or Pulmonary oedema present
• Renal ultrasound
- Renal biopsy – rarely indicated. Indications:
  - Hypertension > 3/52
  - ARF
  - Low C3 > 8 -12wks
  - Nephrotic syndrome
  - Proteinuria > 6 months
    - Microscopic haematuria > 1 yr

  (Renal Scan, coagulation profile etc. if renal biopsy indicated)
Additional indications for renal biopsy in a child presenting with Acute nephritic syndrome

• Features suggestive of a diagnosis other than APSGN:
  - Family hx of glomerular dx
  - Age under 4yrs and over 15yrs
  - Previous hx of similar symptoms
  - Evidence of extrarenal dx
  - Evidence of acute or chronic non-streptococcal infection
  - Atypical investigation results- Low C4, Positive ANCA, ANA, anti-dsDNA, anti-GBM antibodies
  - GFR < 50% of N for age
Confirmatory tests:

a. culture streptococcus – throat swab or skin swab

b. serology (indirect):

   (i) Antistreptolysin 0 titre (ASO titre)
       - starts to rise in the 1\textsuperscript{st} 10 days
       - reaches a peak in 4/52
       - and tails off in 6/52
       - ASOT > 333 Todds Unit markedly raised, <166 normal
       - More raised in pharyngitis - related AGN

   (ii) Anti-hyaluronidase – higher in Pyoderma than pharyngitis associated AGN

   (iii) Anti-deoxy ribonuclease B - raised in both but more in pyoderma
        If (i) to (iii) elevated, sure of diagnosis

   (iv) +ve Streptozyme test – a slide agglutination test that incorporates the
        above. Uses a mixture of extracellular products of the streptococcus.
• 1. Post infectious AGN

Bacteria- Staph, other Strept, Typhoid, Secondary Syphilis, Meningococcaemia etc

Mycoplasma

Post viral AGN – Echovirus, Coxsackie, Varicella, Mumps, Influenza, Hepatitis B&C, Parvovirus etc.

Parasitic – Malaria

Toxoplasmosis
2. Berger’s disease:- (IgA Nephropathy)
   (Benign recurrent Haematuria)
   • The most common chronic glomerular dx worldwide.
   • Episodes of haematuria often pptated by non-specific viral resp. infections or febrile episodes.
   • Present with gross haematuria within 1-2 days of an apparent viral URTI.
   • Latent period of 1-2 days cf 7-21 days of PSAGN.
   • Males are more commonly affected than females
   • Progressive disease develops in about 30% of patients
   • Poor prognosis with hypertension, reduced renal function and severe proteinuria between episodes
   • Immunosuppressives may be beneficial
• 3. Henoch Schonlein purpura  
  - abd symptoms, abdominal pain, intussuception, purpuric lesions  
  - features of G/N

• 4. SLE

• 5. PAN (Polyarteritis Nodosa)
Based on haematuria

1. Haemolytic uraemic syndrome (HUS)
   - Renal failure ± oligonuria –
   - Microangiopathic haemolytic anaemia (fragmented red cell seen in blood film)
   - Thrombocytopenia
   - Commonest cause of ARF now among young caucasian children

2. Hereditary or familial disorders
   - Hereditary nephritis with deafness ALPORT Syndrome
   - Familial Benign recurrent haematuria (good prognosis)
   - Polycystic kidney dx.
Treatment Strategies for AGN

1. Essentially supportive
   Bed rest as necessary
   Fluid and salt restriction
Specific intervention for the following:
   – Hypertension and other signs of volume overload, including encephalopathy
   – Hyperkalemia
   – Acidemia
   – Hyperphosphatemia
• Confirm likelihood of poststreptococcal disease
• Watch for onset of recovery within 7 days
• Keep high index of suspicion for disease other than acute poststreptococcal GN
• Penicillin x 10/7
  - ? Stop further Ag/Ab complex formation, I.M. procaine Penicillin once daily 25-50,000 I.U/kg body weight/day. - If allergic to penicillin – give Erythromycin

• Strict input/output monitoring

• monitor B.P closely; Weigh regularly

• ARF: fluid restriction (300-400mls/m2/day + previous days’ output)

• Antihypertensives:
  - hydralazine – up to 0.5mg/kg stat, 0.15-0.3mg/kg 4-6 hrly
  - Reserpine 0.02 – 0.07mg/kg/day
  - Ca2 + channel blockers (Nifedipine) 0.3-0.5mg/kg/dose
- Hypertensive encephalopathy:
  can use Ca2+ channel blockers e.g. Nifedipine or Diaxozide
given at 3 -5mg /kg /push rapidly or by infusion

• I.V lasix at 1-2mg/kg/dose

• Diuretics:- in mild dx give a thiazide (HCT) otherwise frusemide

• Hyperkalaemia
  - iv Calcum gluconate 10% (>6.5mEq/L with ECG changes)
  - IV NaHCo3
  - Glucose/insulin
  - Ion exchange resin
  ± Dialysis
Prognosis

- Prognosis is good
- 80% recover completely
- 10% may go into CRF, so follow up for up to adulthood
Pathology

- Glomeruli enlarged and globular
- Cellular proliferation - increased number of cells in the glomerular tuft, endothelial, mesangial and epithelial cells
- Leucocyte proliferation - neutrophils, monocytes within glomerular capillary lumen
- GBM thickening
- Hyalinization/Sclerosis – irreversible
- Electron dense deposits – immune complexes
NEPHROTIC SYNDROME
Nephrotic Syndrome is characterised by:

(i) Heavy proteinuria
   - >50mg/kg/day in a 24hr sample
   - or >40mg/m²/hr
   - or early morning urine protein: creatinine ratio >200mg/mmol

(ii) Hypoproteinaemia < 2.5gm/dl

(iii) Massive generalised oedema

(iv) Hyperlipidaemia
   - (Cholesterol > 220mg/dl)

It is a feature of a number of kidney diseases, not a disease entity on its own

Normally protein loss = <150mg/day
TESTING FOR PROTEINURIA

- Urine dipstick: quantitative screening method.
  Reagent: Tetrabromophenol blue
  Primarily detects albumin
- Does not differentiate between glomerular and tubular proteinuria.

<table>
<thead>
<tr>
<th>Dipstick</th>
<th>Protein concentration (mg/dl)</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trace</td>
<td>-15</td>
</tr>
<tr>
<td>1+</td>
<td>-30</td>
</tr>
<tr>
<td>2+</td>
<td>-100</td>
</tr>
<tr>
<td>3+</td>
<td>-300</td>
</tr>
<tr>
<td>4+</td>
<td>≥2000</td>
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Testing for Proteinuria

• **Timed urine collection**: Accurate measurement of protein excretion. 24-or 12-hour (overnight) urine prot. excretion:

• Children: varies with age and size (BSA).

  Protein excretion:
  
  \[
  \begin{align*}
  &< 4\text{mg/m}^2/\text{h} & \text{normal} \\
  &4-40\text{mg/m}^2/\text{h} & \text{abnormal} \\
  &>40\text{mg/m}^2/\text{h} & \text{nephrotic range or 1g/m}^2/\text{day}
  \end{align*}
  \]

Normal protein excretion: \(< 100\text{mg/m}^2/24\text{h}\) *

* Denotes approximate values for normal protein excretion.
Testing for Proteinuria

• **Alternative:**

  Spot urine Protein/creatinine ratio (mg/mg).
  First morning urine specimen (ideal)

  **Normal values**
  6 months- 2 years of age: < 0.5
  Children older than 2 years: < 0.2
  Unreliable if: severe malnutrition or reduced GFR

  **Nephrotic range proteinuria** - Urine Protein/Creat. Ratio ≥ 2.0
Excessive loss prevented by:

Molecular size
- Mol wt >60,000 daltons excreted minimally

Molecular charge
- Net negative charge on glomerular capillary wall retarding polyanions e.g. albumin>neutral & +vely charged ones
  
  (Sialoproteins & glycosaminoglycans in GBM → glomerular polyanions)

Stereochemistry of the protein → deformability

Haemodynamic factors
- esp. those producing alterations in GFR & glomerular capillary flow.
PATHOGENESIS OF CLINICAL FEATURES
HYPOPROTEINAEMIA

1. Immunologic damage to the filtration pit → excessive loss of protein
   - Remarkable changes occur in serum albumin & plasma proteins of similar molecular characteristics as albumin → Low serum Albumin, Transferrin, anti-Thrombin III, Factor B of the complement system etc.
   - Serum proteins of ↑sed value in N/S - α2 globulin
     - Pre-beta lipoprotein
     - β-globulin
     - fibrinogen

2. ↑sed tubular catabolism of albumin
OEDEMA

i. Excessive protein loss
   → hypoalbuminaemia
   → Low oncotic pressure loss of fluid into the interstitial space ↓
   Intravascular compartment→
   1. ↑ADH secretion → ↑H2O absorption→worsening of oedema
   2. Activation of the Renin – Angiotensin – Aldosterone system →
      ↑Na+reabsorption & water retention
   3. ? Stimulation of the sympathetic Nervous system
   4. ? Suppression of atrial natriuretic peptide → Na+ & H2O retention.

ii. Other explanations
   a. Intrarenal defect in Na+ & water excretion.
   b. Presence of a circulating agent that ↑ses capillary
      wall permeability thro’out the body including the kidneys.
HYPERLIPIDEMIA

(i) Synthesis of albumin is linked with that of lipoproteins by the liver

- In nephrotic syndrome, compensation of hypoalbuminemia → production of albumin & concomitant production of lipoproteins (LDL – cholesterol, VLDL that binds triglycerides)

- Whereas albumin is lost in urine, the lipoproteins b/c of their large mol. wts remain in the serum & bind lipids → hyperlipidaemia

(ii) ↓ Lipid catabolism owing to ↓sed plasma lipoprotein lipase, a major enzyme that removes lipids from plasma.
The nephrotic syndrome is the most common chronic renal disease of childhood.

Amongst the Caucasians, idiopathic nephrotic syndrome constitutes about 90% of their cases, with minimal change nephropathy being responsible for 85% of these.

90% of these children with minimal change nephropathy will respond to corticosteroid therapy although some will have relapses up till the 2\textsuperscript{nd} decade of life. The prognosis amongst them is good.

In Africa, however, the overall picture is characterized rarity of minimal change disease, association with infectious agents, variable but relentless progression to chronic renal insufficiency and a high mortality rate.
• **EPIDEMIOLOGY contd.**

Prevalence figures vary largely. Remains a main indication of referral into specialized children’s ward (2-4 new cases/100,000 population per year)

• The predominant histologic lesions present in a community influence prevalence. Dominance of varying lesions is reported from different centres even in the same country.

• Peak age incidence in most centres in Nigeria occurs in the school age years as against pre-school age reported in Caucasian series.
• There is a male preponderance in many series.

• FSGS and membranous nephropathy (S. Africa) are common in black children as against MCNS in white population.

• Genetic and environmental factors may therefore play some roles in the determination of the diseases pattern and features.
• Focal Segmental Glomerulosclerosis (FSGS) is currently the most common glomerular disorder resulting in End-stage kidney disease in children and young adults in the US and many parts of the world.

• FSGS, especially when steroid-resistant is associated with a very poor prognosis, with 25-30% of the children developing chronic renal failure within 5 years.

• It poses an additional challenge of recurrence post-transplant which usually results in graft loss in over 50% of cases.
AETIOLOGY

Divided into:

- Primary (cause unknown)
- Secondary – Associated with some diseases
Congenital Nephrotic Syndrome

• A heterogeneous collection of 1ry & 2ry dsx that may share only the fact that onset occurs in the 1st 3/12 of life.

• Notable – FINNISH TYPE OF CONGENITAL N/S

• Rare in many parts of the world but has high incidence in Finland/people of Scandinavian descent.

• A-R inheritance; LBW

• Child born with large placenta (placentomegaly-placenta:infant wt ratio > 0.25)

• Present in the 1st 3/12 of life

• No response to steroids/other immunosuppressives.
- Genetic mutation is with NEPHRIN, a membrane protein, a vital component of the slit diaphragm of the glomerular ultrafilter.
- A cause of raised level of alpha fetoprotein in maternal blood and amniotic fluid.
- **N/B - Causes of 2º Congenital N/S:**
  - Syphilis
  - Toxoplasmosis
  - CMV
  - Renal vein thrombosis etc.
PRIMARY

A. MINIMAL CHANGE N/S
   - Under light microscopy not much abnormality seen but electron microscopy shows fusion of the foot processes.
   - Commonest type in Europe & North America.

B. MEMBRANOPROLIFERATIVE G/N
   - Diseases of the B/M with some proliferation of the mesangial cells & endothelial cells.
   - Immune complexes deposited on the subendothelial aspect of B/M (Most of our cases are of this histologic type although 2°)

C. MEMBRANOUS NEPHROPATHY
   - Immune complexes deposited on the subepithelial aspect of the capillary B/M spikes of basement membrane-like material.
   - (Some cases of P.malariae nephropathy have this histologic picture & also SLE) → Hepatitis B associated nephropathy).
Minimal change Dx
Normal glomerulus

- Basement Membrane
- Endothelium
- Red Blood Cell
- Podocytes
- Foot Processes
- Endothelial Cells
- Mesangial Cells
- Mesangial Matrix
Minimal change ds-effacement of foot processes on EM
Membranous
Membranous

http://www.unckidneycenter.org/kidneyhealthlibrary/membranousg.html
D. FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

- Could be classified as Primary, Secondary, familial or syndromic.
- The primary FSGS is similar to MCNS in presentation but has a poorer prognosis
- Could respond to steroids initially
- Seen in D/M, HIV

N/B

- Human FSGS or Nephrotic Syndrome Genes
- NPHS2 (encoding Podocin) – Steroid resistant NS (recessive)
- NPHS1 (encoding Nephrin)- Congenital NS (recessive)
- ACTN4 ( encoding Alpha-actinin-4)- Familial FSGS ( dominant)
Focal segmental glomerulosclerosis
FSGS-trichome
Incidence is 3 times more common in Blacks than in Whites and particularly high in adolescents.
Renal Survival: Glomerular Tip Lesion (n=34) vs. Collapsing FSGS (n=15) vs. Typical FSGS (n=48) (Jennette [Appel ‘03])
E. PROLIFERATIVE G/N - different types:

1. Diffuse-post strept. AGN
2. Focal proliferative
3. Mesangial-1gA deposits
4. Mesangiocapillary (MPGN)
5. Crescentic
SECONDARY N/S

1. Post-Infectious
   (i) Protozoal

   (a) *P. malariae* (QMN)
       - Very important here.

       - In late 1960s, 80% of pts with N/S in Ibadan, ¼ of cases seen in Zaria

       - No typical histologic picture currently accepted
       - More of membranoproliferative G/N
Xteristic lesion of QMN

- Consists of capillary wall thickening

- Segmental glomerular sclerosis

- Leads to progressive damage & 2° tubular atrophy

- Cellular proliferation is inconspicuous or absent

- A unique feature is presence of small lacunae scattered throughout the basement membrane often containing islands of material similar in density as B/M.

- QMN is an immunologically mediated disorder initiated by quartan malarial infection and which once established pursues a progressive course.

- Graded into I, II & III depending on severity of glomerular affectation.
(b) P. falciparum – Rarely

© Toxoplasmosis

(ii) PARASITIC
   (a) S. mansoni,
   (b) sometimes S. haematobium,
© filariasis

(iii) VIRAL
    (a) Hepatitis B,
    (b) CMV,
    (c) Varicella,
    (d) HIV

(IV) BACTERIAL
    (a) Post-Strept. AGN
    (b) Syphilis, rarely
© Infective endocarditis,
    (d) shunt nephritis.
2. **Multisystemic & Connective Tissue Diseases**
   - SLE, Henoch-Schonlein
   - Purpura, Sarcoidosis
   - Amyloidosis.

3. **Allergic Disorders:**
   - Bee sting, serum sickness,
   - Pollens, poison oak
   - Poison ivy

4. **Drugs & Heavy metals**
   - Hg – bleaching cream
   - Pb
   - Gold-Rx of rheumatoid arthritis
   - Penicillamine-Wilson’s Dx
   - Trimethadione – Petit mal epilepsy
   - Improves with drug withdrawal
5. Neoplastic-lymphomas,
   -leukaemia,
   -Wilms’ tumour

6. Heredofamilial disorders
   -SCA
   -Alport’s Syndrome
   -Nail-Patella syndrome

7. Metabolic Disorders
   – Diabetes Mellitus
   -Hypothyroidism

8. Miscellaneous
   – congestive cardiac failure

9. Transplant rejection
CLINICAL FEATURES

1. Oedema
   - Usually starts from the face (periorbital swelling) limbs, abdomen, genitalia.
   - subsides with ambulation & persistent later.
   - Wt. increase in spite of poor appetite
   - Pts present about 1-2 months after onset of symptoms.

2. ± ↓ urinary output

3. Abd. Swelling due to ascites

4. ± Pleural effusion

5. Features of infection

6. BP – Usually (N) in the early stages but in some types e.g. MPGN could be raised
INVESTIGATIONS

✓ URINALYSIS:
   Proteinuria +++ or ++++
   Blood, sugar – Transient Tubular – dysfunction, D/M.

✓ Urine Microscopy
   RBC, WBC – Casts

✓ stools – S. mansoni ova

✓ E/U-
   Na+, Cl, K+, HCO3 usually normal
   Na+ may be low or normal,
   Urea normal,
   Ca - Ionised Ca-2+(N) But total Ca2+ reduced,
   Creatinine (N)

✓ Renal biopsy

✓ G6pd assay
PROTEIN SELECTIVITY

- Glomerulus seen as a sieve

- With renal lesions showing only minimal changes, albumin is lost mainly
  - (Highly selective proteinuria).

- Lesions with marked histological changes lead to loss of larger molecules in addition to albumin
  - (Poor selectivity)

- Adeniyi et. Al utilised: Protein Selectivity Index
  Clearance of IgG /clearance of Alb x 100
  1-15% – Highly selective
  15-30%- Moderately selective
  > 30% - Poorly selective
Renal Biopsy

- Percutaneous renal biopsy is an invasive procedure, the benefits should outweigh its risks.
- It is useful in making a diagnosis, planning treatment and in prognostication.
- The indications for Renal Biopsy in Children with Nephrotic syndrome include:

  ➢ All the nephrotic patients presenting in our environment (since most are steroid resistant) who have no contraindication to renal biopsy

  ➢ In Caucasian children - Aged less than 1 year or over 10 years of age (since more than 90% chance of having minimal change Nephropathy)

  ➢ Those with low serum complements

  ➢ Failing corticosteroid therapy
Treatment

• SUPPORTIVE

  – Weigh daily, monitor BP, urinalysis.
  – Monitor input/output
  – DIURETICS – Mild, not fast acting ones – Thiazides preferred.
  – 2° hyperaldosteronism - Spironolactone

• DIET
  – Protein of high biologic value
    - Normal intake if renal function normal.
    - Cholesterol & saturated fatty acids be curtailed

• Modest exercise to discourage thromboembolic phenomena

• No femoral tap.
Resistant oedema

- Salt-poor Albumin Infusion 1g/kg daily or 2ce daily over 4hrs + IV Frusemide 1-2mg/kg after 2hrs
- or
- FFP 10mls/kg 12 hrly & wait for 30 mins & give Frusemide IV.
- Metolazone + Frusemide – requires admission & close monitoring.
• **Nephrotic syndrome**: Edema, plasma albumin < 25 g/L; proteinuria > 40 mg/m2/hr or protein: creatinine ratio > 200 mg/mmol.

• **Remission**: Urinary protein excretion < 4 mg/m2/hr or Albustix = O/trace for 3 consecutive days.

• **Relapse**: Urinary protein excretion > 40 mg/m2/hr or Albustix = ++ or more for 3 consecutive days, having previously been in remission.

• **Steroid responsive**: Remission achieved with steroid therapy alone.

• **Late responder**: Remission occurring after 4 weeks prednisolone 60 mg/m2/day without other drugs.
• **Frequent Relapses:** Two or more relapses within 6 months of initial response or 4 or more relapses within any 12 months period.

• **Steroid dependence:** Two consecutive relapses occurring during corticosteroid treatment or within 14 days of its cessation.

• **Steroid resistance:** Failure to achieve response inspite of 4 weeks prednisolone 60 mg/m2/day

• **Early non-responder:** Steroid resistance in the initial episode.

• **Late non-responder:** Steroid resistance developing in a patient who had previously been steroid responsive.
SPECIFIC

• MINIMAL CHANGE (STEROID SENSITIVE NEPHROTIC SYNDROME)
• LEVELS OF MANAGEMENT
  – 1. Initial episode
    Pred 60mg/m²/day x 4 wks (max 80mg/day), then 40mg/m² on alt days x 4wks (3-7 months)
  ↓

2. First two relapses
Pred 30mg/m²/day until remission, then 40mg/m² on alt days x 4 wks (3-7 months)
    ↓

3. Frequent relapses
Maintenance pred 0.1-0.5mg/kg/alt day for up to 12 months
    ↓

4. Relapse on prednisolone
   > 0.5mg/kg/alt day
Levamisole 2.5mg/kg/alt day for 4-12 months (6-24 months).

5. Relapse on prednisolone
And
Steroid side effects or risk factors
 or
 Relapse on prednisolone
 >1mg/kg/alt day
 Cyclophosphamide 3mg/kg/day x 8wks or 2mg/kg/day for 12wks

down
6. Post cyclophosphamide relapses
7. As in 2-3 above
8. Relapse on/post cyclosporine

(Modified from the British Association for Paediatric Nephrology and Research Unit Royal College of Physicians.)
STEROID RESISTANT NEPHROTIC SYNDROME

MORE AGGRESSIVE REGIMEN

• Combination of vincristine, cyclophosphamide and prednisolone

• “Mendoza” regime (prolonged course of IV methylprednisolone) eg pulse methylprednisolone, oral prednisolone ± cyclophosphamide or chlorambucil.

Cyclosporine, Mycophenolate mofetil, Tacrolimus,

OTHERS

Mercaptopurine, indomethacin, plasmapheresis, pefloxacin, intravenous Immunoglobulins, ibuprofen, Chinese herbal medicines – remission rate is low.
COMPLICATIONS

1. **Malnutrition-direct consequence of urinary protein loss**
   - Aggravated by anorexia and vomiting.

2. **Increased susceptibility to infections**
   - A. ↓Immunoglobulins
   - B. Oedema fluid acting as a culture medium
   - C. Protein deficiency
   - D. ↓bactericidal activity of leucocytes
   - E. Immunosuppressive therapy
   - F. ↓perfusion of the spleen due to hypovolaemia
   - G. Loss in urine of factor B (Alternative pathway particularly significant in the opsonization of encapsulated organisms.)
Complications (contd)

3. **Hypercoagulable state**
   - Imbalance b/w factors that promote coagulation (elevated fibrinogen, Factors V and VIII and factors that normally inhibit coagulation. There is urinary loss of Anti-thrombin III).
   - There are hyper-aggregable platelets and blood viscosity is raised by haemoconcentration.

4. **Loss of transport proteins** e.g. Vitamin D binding protein

5. **Chronic Renal Insufficiency and Failure**

6. **Hyperlipidaemia** – increased risk of ischaemic vascular disease
TX OF COMPLICATIONS

- Infection– Antibiotics
- Thromboembolism– Correct hypovolemia, - heparin.
Vaccination

- Polyvalent Pneumococcal vaccine should be administered.
- Zoster immunoglobulin would be needed if there is exposure to *Herpes zoster*.
- Acyclovir could be administered if there is serious treat of chicken pox.
- Another threat is measles infection, which could be treated with gamma globulin.
- Live vaccines should be avoided when steroid therapy has been commenced unless low dose steroid is being given.
- Killed vaccines however could be administered. Live vaccines should also be avoided when alkylating agents are being given.
Differential Diagnosis

• AGN
• Kwashiorkor
• CCF
• Chronic Liver disease
• Beri-beri
PROGNOSIS

• Variable

• Quartan Malarial Nephropathy
  – Poor
    - Develop Hypertension with End – stage Renal Disease within 5 to 7 years.

• Minimal Change Disease
  – Better outcome
    - May have relapses till the 2\textsuperscript{nd} decade.