GLOMERULONEPHRITIS in CHILDREN

CHRONIC KIDNEY FAILURE

Plan of the lecture

- 1. Definition of glomerulonephritis
- 2. Risk factors and etiology
- 3. Pathogenesis
- 4. Classification
  5. Diagnostic criteria
- 6. Treatment and prophylaxis

Glomerulonephritis (Gn): definition

- **Gn is heterogeneous group of inflammatory immune-complex diseases predominantly of kidney glomerular apparatus with different clinical and morphological presentation, course and outcome.**

Epidemiology

- Glomerulonephritis take 3-4 place among all urinary tract diseases;
- Morbidity is more frequent in 3-12 years old, but children of all ages can be affected. If glomerulonephritis occur after 10 years old it is more frequently chronic form or resistant for steroid therapy.

Etiology

- Any diseases that are caused by Streptococcal infections of group A : 4, 6, 12, 18, 25, 49 strains (like angina, scarlet fever, piodermia);
- Viral infections (adenoviral, flu, ECHO 9, Cocsakie, Varicella, epidemic parotitis);
- Autoantibodies for mesangeal epithelial, basal, nuclear antigenes;
- Noninfectious factors: overcooling, repeated vaccinations and serum medications injections, trauma, insolation, some medications that release autoantigenes;
- Idiopathic (IgA-nephropathy, membranous-proliferative glomerulonephritis of I-II types).

Pathogenesis

- Main mechanism is immunopathologic reactions;
- There are 2 main mechanisms: immunocomplex (in 80-85%) and autoimmune;

Immuncomplex glomerulonephritis factors

- Disturbances of immune complexes clearance from circulation;
- Compliment system pathology that leads to impairment of immune complexes inhibition;
- Disturbances of erythrocyte clearance of immune complexes due to pathology of CR1-receptors in erythrocytes;
- Functional blockage of mononucleal phagocutes Fc-receptors in liver and spleen;
- Excess of immune complexes formation with peculiar sizes and charge that capable connect with target organs and tissues

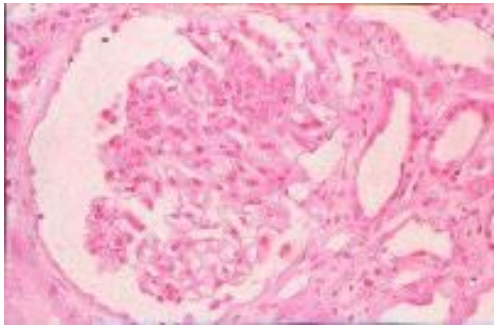
Autoimmune mechanism of glomerulonephritis development differs from immunocomplex process only by its initial steps. Effector process is common due to:

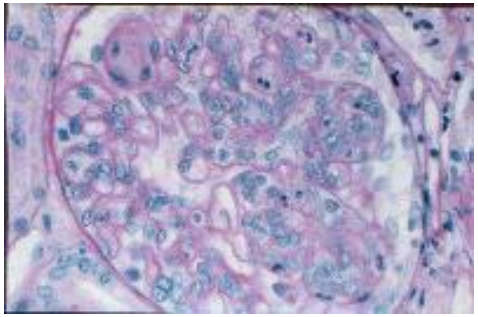
- Presence of common criss-cross antigenes of microorganisms (bacteria, viruses) and basal membrane and absence of tolerance;
- Appearance of HLA complexes (DR2 и DR3)on glomerular basal membrane;
- Kidney tissue damage and releasing of hidden antigenes or glomerular membranes dterminants that has no immune tolerance.

The only necessary condition for glomerulonephritis development due to autoimmune mechanism is specific immunodefficiancy with decreased function of T-supressors.

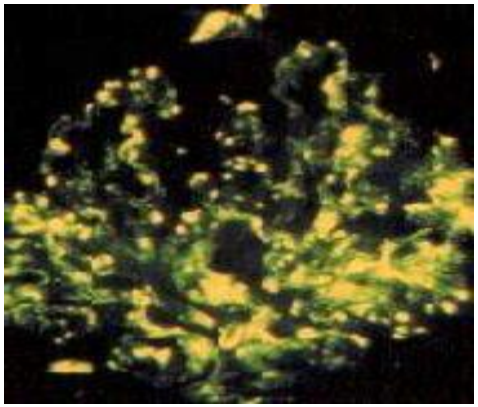
Morphologic forms of glomerulonephritis

- **Minimal glomerular changes: increased cellularity, basic substance, basal membrane edema, podocyte peduncuy destruction, but absence of Ig and fibrinogene deposits like in nephrotic syndrome**





- **Focal-segmental glomerulosclerosis/gyalinosis: more frquently juksta-glomerular parts are affected (Berge disease or Ig-A nephropathy)**



- **Diffuse Gn (80% and more glomerulus are affected)**
  - ***Membranous Gn:*** **diffuse uniform capillary walls thickening in glomerulars without cell proliferation and matrix increasing but with thorn development on basal membrane;**
  - ***Diffuse proliferative***
  - **Mesangiocapillary Gn**
    - **Mesangeal proliferative Gn**
    - **Endocapillary proliferative**
- **Fibroplastic Gn**
- **Gn with semilunaris (crescentic) (subacute fast progressive Gn)**

Classification of primary glomerulonephritis

ACUTE GLOMERULONEPHRITIS:

- **Nephritic syndrome;**
- **Isolated urinary syndrome;**
- **Nephrotic syndrome;**
- **Nephrotic with hypertension and hematuria**

CHRONIC GLOMERULONEPHRITIS:

- **Hematuric form;**
- **Nephrotic form;**
- **Mixed form.**

SUBACUTE (MALIGNANT) GLOMERULONEPHRITIS

Process course activity

Acute Gn

- Initial manifestation;
- Swing period (2-4 weeks);
- Period of clinical regression (2-3 months).

Chronic Gn

- Period of exacerbation;
- Period of partial remission;
- Period of complete clinic-laboratory remission.

Kidney functioning condition

Acute Gn

- Without impairment;
- With kidney functioning impairment;
- Acute kidney failure.

Chronic Gn

- Without impairment;
- With kidney functioning impairment;
- Chronic kidney failure.

NEPHRITIC SYNDROME

- Morbidity is frequent at 5-12 y old;
- Streptococcal diseases of oral cavity and skin as a rule precede 2-4 weeks before Gn onset;
- Onset of Gn is sudden with intoxication signs like head ache, malaise, nausea

- Paleness of skin (due to angiospasm)
- Loin pains (due to kidney capsule distention because of parenchyma edema)
- Moderate edema of face, low extremeties;

- Cardio-vascular abnormalities- tachycardia;
- Arterial hypertension;
- Oliguria can occur;
- Hematuria (micro or macrohematuria);

- Proteinuria not more than 1-2 g/l per day;
- Frequently moderate anemia, ESR elevation, leucocytosis (if infectious focus is present) can be present
- Dysproteinemia, ASL”O” more than 250 IU, hyperfibrinogenemia;
- Kidney function insufficiency can be present

Isolated urine syndrome

- **Onset is steady without any subjective symptoms and extrarenal signs. There are only urine changes like hematuria, moderate proteinuria, cylindruria**

NEPHROTIC SYNDROME

- Typical for preschools (1,5-5 y old)
- Frequently family history has allergologic anamnesis;

- **Onset is steady with edema development that can be excessive. Edema can be peripheral, cavitary, and very significant like anasarka. Sudden onset is possible.**

- Olyguria
- Significant proteinuria more than 3 g/l per day.;
- Blood tests – hypoproteinemia predominantly due to hypoalbuminemia, high hyperlipidemia and cholesterolemia, hyperfibvrinogenemia;
- ESR is elevated to 50-70 mm/h

NB !

BP is normal, hematuria isn’t present, kidney function failure isn’t typical

Standards of lab testing

- **Obligatory lab studies**
  - Common blood test +thrombocyte count;
  - Biochemical tests (proteinogram, cholesterol, creatinine, urea etc.);
  - Common urine tests;
  - Daily diuresis with daily protein loss;
  - Nechiporenko test;
  - Zimnitsky urine test;
  - Immune tests (ASL-O, CIC, IgM, IgA, compliment system).

- **Specifying tests (if necessary))**
  - **Blood electrolites (in stimulated urination, corticosteroid treatment)**
  - **Liver tests (especially in cytotoxic drugs treatment)**
  - **Glucose tests (corticosteroid treatment);**
  - **Coagulative tests (desaggrigant, anticoagulative therapy, DIC -syndrome);**
  - **Daily proteinurea (in case of protein losses);**
  - **Creatinine clearance (if kidney function is impaired);**
  - **Uroleucogram and bacterial culture tests of urine (if leucocyteurea is present).**

Additional lab tests

- Of blood
  - Antibodies to glomerular basal membrane and neutrophyl cytoplasm (ANCA);
  - Lipidogram;
  - Acidic-basic ratio;
  - Kidney functioning tests;
  - Fibrin products degradation (protaminesulphate and ethanol tests);
  - Antinuclear antibodies, LE-cells;
  - HLA-typing;
  - Markers of hepatite testing;
  - Etc..
- Urine
  - Osmolality testing
  - B-2-microglobuline studying
  - Lysozyme detection
- Throat
  - Streptococus smears
  - Microscopy of buccal washings
- Stool
  - Coprogram

Obligatory instrumental testing

Type of testing	Gn stage	Frequency
BP monitoring	Exacerbation Regression period Remission period	Every day 2 times/week If necessary
Body weighing	In edema	Every day
Mac-Klur test	In hidden edema	If necessary
Retina examining	In exacerbation period, while treating by delagyl	Every day
ECG	In exacerbation In other cases	Every day If necessary
Ultrasound of kidneys and UT	Swing period Regression period Remission period	Once Once If necessary
Ultrasound diagnostics of inner organs	Swing period In other cases	Every day If necessary
X-ray of bones, lungs	-	If necessary
Radionuclide examining	Swing period In other cases	Twice Once per 1-2 years
Punction kidney biopsy	Before treatment After treatment Before finishing outpatient care	Once Once Once

Glomerulonephritis treatment

Regimen is strictly bed type only if extrarenal symptoms are present like edema, hypertension, olygouria, macrohematuria

–Diet

Is dependant on edema arterial hypertension and functional kidney capacity. During acute period salt (NaCl) must be excluded, fluids and animal proteins must be restricted. All these demands are taken into account in diet N7 (Pevzner)

Medications:

- a) etiologic (if infection as initializing factor is proved or chronic focus of infection is present-antibiotic treatment (preferably penicillines);

- b) pathogenic (the main goal is to eradicate antigen from organism and supress antibody production)
- Plasmopheresis or hemasorbtion (if creatinine, urea level, hyperfibrinogenemia and circulated immune complexes (CIC) are increased

- **disaggregegants** (curantil, ticlid) for 3-4 weeks 2-5 mg/kg per day, than 1/2 of this dosage for 1-3 month;
- **anticoagulants** (heparin 50-150 IU/kg 4 times per day with blood coagulation tests control (Lee-White test);

- **Corticosteroids** 1,5-2mg/kg per day, prednisolon for 8 weeks than cyclic treatment with 1/2 of initial dosage with steady decreasing of it for 2,5-5 mg once per 1,5 - 2 month;
- **Cytostatics** (leukeran 0,2 mg/kg per day for 6-8 weeks, than 1/2 of initial dosage for 6-8 months).

- **Antihypertension, antiproteinuric, antisclerotic drugs :**
- **Angitensin converting enzyme inhibitors (ACEI) –enalapril, lysinopril – 5-40 mg/day; Angiotensin receptor blockers (ARB) - (candesar, telmisartan)**
- **Ca channel blockers- diltiazem**
- **в) syndrome therapy: diuretics (trifas,lasycs,hypothiazid,verospironi).**

Outpatient care

- **After acute glomerulonephritis clinical-laboratory remision children must be for 5 years under outpatient medical care**

Subacute rapidly progressive (crescentic) GN

- Crescentic GN is severe form of glomeruli injury with presence of large crescents in 50% and more glomeruli. The condition presents with severe acute GN with azotemia that fails to resolve. It can occur in poststreptococcal GN or features of nephrotic syndrome.The long-term outcome dependsof therapy efficiacy and its promptness.

Chronic kidney diseases

From 2003 concept "Chronic kidney disease" was introduced to children nephrology

Criteria of CKD:

1. **Lesion of kidneys more than 3 months with structural or functional features with or without glomerular filtration rate decreasing and manifested by one or several symptoms listed below:**
    - **Urine test or blood test changes;**
    - **Visualizing changes during special examinings;**
    - **Biopsy changes.**
2. **Glomerular filtration rate less than 60 ml/min or 1,73 м2 for 3 months with or without other kidney damages.**

- **CKD can be independent diagnose or summerized one;**

  Like:

  - **CKD**
  - **CKD: chronic glomerulonephritis, hematuric form, clinic-lab remission period.**

- **Diagnosting of CKD is performed independently to causative disease.**

  In this situation we suppose further process progression even without glomerular filtration rate decreasing

Risk factors for CKD development

- CKD induced factors
  - **Diabetes mellitus 1, 2 type;**
  - **Arterial hypertension;**
  - **Autoimmune diseases;**
  - **Urinary tract infection;**
  - **Nephrocalcinosis;**
  - **Toxic medication influences.**

- **Factors induced CKD progression**
  - **High level of proteinurea or arterial hypertension;**
  - **Insufficient glycemia level control;**
  - **Smoking.**
- **Risk factors of CKD end-point**
  - **Low dialyze access;**
  - **Temporary vessel access;**
  - **Anemia;**
  - **Low level of albumin;**
  - **Late dialyze treatment.**

Glomerular filtration rate

- **GFR less than 60 ml/min – can be developed due to CKF without clinical- lab symptoms of kidney disease.**

- **GFR less than 60 ml/min means that more than 50% of nephrones has been destroyed, but creatinine level can be in the highest normal level.**

Formula for GFR calculation

After author of formula (quantity of studied patients)	Formula with usage of serum creatinine level and height
Schwartz other (n=186)	**[0,0484 * height(sm)]** **CCr (ml/min/1,73m2) = ----------** **Scr(mMol/l)** For boys more than 13 years old substitute coefficient 0,0484 for 0,0616
Konegen and other. (n=108)	**[0,043 * height(sm)]** **CcR*(ml/min/1,73м2)= ----------** **Scr(mg/dl)**
Ccr – creatinine clearance, Scr – serum creatinine.	

*** - in online regimen calculations of GFR according Schwartz formua is accessible in Internet: www.nephrology.kiev.ua**

Hystologic types of CKD

- Proliferative GN (mesangial prolifirative GN, crescentic GN, membranoproliferative GN)
- Focal segmental glomerulosclerosis
- Membranous nephropathy with diffuse thickening of glomerular basement membrane

CKD treatment

- There is no specific treatment for chronic GN.
- Steroids and immunosuppressive drugs can only retard development of renal sclerosis and progression to chronic renal failure

Chronic kidney failure

is stable irreversible progressive kidney function disorder due to different diseases manifested by endogene createnine clearence decreasing more than 20ml/min 1,73 m, serum createnine more than 0,177 mmol/sec, urea more than 5,8 mmol/l

(4 European Congress of pediatritians-nephrologists Recommendations, Dublin, 1971)

CKD and CKF classification

CKD stage	CKF stage	GFR мл/мин/1, 73 м2	Blood creatinine, mMols/l	Max urine spec. gravity
I	-	≥90	≤0,104	›1,018
II	I (tubular) I (compensated)	≥90 89-60	≤0,104 0,105-0,176	≤1,018 ‹1,018
III	II (subcompensated)	59-30	0,177-0,351	‹1,018
IV	III (decompensated)	20-15	0,352-0,440	-
V	IV (terminal /dialyzed)	‹15	›0,440	-

2.Total kidney failure

Serum createnine content 0,17 –0,44 mmols/l:

***Glomerulopathies*: Hypertension, hemorrhagic syndrome, acidosis, decreasing of glomerular filtration rate and tubular functions**

***Tubulapathies*: osteopathies, anemia, acidosis, glomerular filtration rate and tubular function limitation**

Serum createnine level is 0,44-0,88 mmol/l in first group disturbancies of inner organ functioning, in tubulopathies both inner organs functioning and hemorrhagic syndrome will be present

If createnine concentration is more than 0,88 mmoll/l symptoms of uremia will be present. This is End Stage Renal Disease, olygoanuric stage

Chronic kidney failure (CKF) etiology

- Glomerulopathies: Primary glomerular dieases, immuneglobuline A nephropathies, membrane-proliferative glomerulonephritis
- Glomerulopathies associated with systemic diseases – diabetus mellitus, amyloidosis, SLE, hemolytic-uremic syndrome
- Tubularinterstitial disease:reflux-nepohropathies with pyelonephritris, sarcoidosis, toxic nephropathies
- Inherited diseases: cystic, Alport syndrome
- Hypertension
- Kidney vascular disesases
- Obstructive uropathies

CKF syndromes and reasons of their development

- **Failure to growth and development – hypostature, malnutrition, sexual development retardation due to kidney dysembryogenesis, nephrosclerosis, protein and vitamin defficiency, azotemia, acidosis**
- **Uremia - astenia, anorexia, psychoneurologic disorders, gastroentherocolitis, pericarditis due to retention of nitrogenic metabolites and impaired filtration, enhanced catabolism**
- **Water and electrolite balance disorder –edema, hyperkaliemia, hypocalciemia, hyponatriemia due to glomerulo-tubular dysbalance and impaired electrolyte transport**
- **Metabolic acidosis - nausea, vomiting, dyspnea due to impaired ammonia- acid filtration, exhausting buffer reserve**

- **Arterial hypertension - head ache, hypertonic crises, retinopathy due to enhanced Pg production and water –electrolyte dysbalance**
- **Osteodystrophy – pains in bones, X-ray and morphologic changes due to impaired VitD metabolites synthesis and hyperparathyroidism**
- **DIC syndrome – Hemorrhagic lesions in different organs and tissues due to impaired thrombus formation, rheology, coagulative disorders**
- **Immune-deficience –frequent viral and bacterial infections, septic complications due to protein deficiency, hormonal dysbalance**

Diet in CKF

- **Diet N 7 : moderate limitation in protein, salt (not more than 0,4 g/day). Restrict meat, fish, cottage cheese**
- **May eat potato, oils, eggs, sour-cream, bread, pasta**
- **Day quantity of proteins 0,6 до 1,7 mg/kg per day**

In 3-4 grade of CKF protein intake mustn't exceed - 0.5 g/kg per day

- **Essential amino-acids can be used as food additives (ketosteril – 1 trabl/kg per day)**

Hemodialysis

- **Indications:**

Glomeruli filtration rate less than10 ml/(min for 1,73sq.м), createnine more than 0,7 mmols/l , hyperkalemia more 6,5 mmol/l, «noncontrolled» hypertension, uremic pericarditis

- **Cointraindications:**

Multiple malformations, malignancy, law birth weight, tuberculosis, hepatitis, GI ulceration parents refusal

- **Indications for kidney transplantation terminal kidney failure stage**
- **Contraindications : mental diseases, malignancies, sepsis, chronic purulent lung diseases, systemic vasculitius, reflux-nephropathy, ulcer stomach diseases, polyserositis, severe uncontrolled hypertension**

Questions

- Glomerulonephritis and chronic kidney failure.
- Classification glomerulonephritis and kidney failure in children.
- What causes glomerulonephritis?
- What causes acute and chronic kidney failure?
- Clinical forms glomerulonephritis.
- Clinical manifestations. Diagnosis.
- Can medicine treat glomerulonephritis?
- Rational antibiotic and hormone treatment.
- Transplantation of kidney.