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TITLE: **CHRONIC GLOMERULONEPHRITIS**

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CHRONIC GLOMERULONEPHRITIS

Etiology

In most of cases the etiologic agent remains unclear. It is acceptable, that in 20% beta-hemolytic streptococcus from group A are the cause for the development of the disease. In the rest 80% of cases the possible agent could be: other bacteria – Gram- positive or Gram-negative - staphyllo-, meningo-, pneumo-, enterococci and oth.; Riketsia and viruses such as the agents of hepatitis, small pox, abdominal typhus, grippe, herpes, HIV, Epstein-Barr, Cytomegalovirus; Fungi - Candida, Histoplasma capsulatum, Coccidioides; Parasites – plasmodium malariae, Toxoplasma gondii, Trypanosoma; Drug and chemical agents (volatile hydrocarbons and solvents), heroin, serums, vaccines.

Immunopathogenesis of renal disease

The mechanisms of renal injury that lead to progressive disease are becoming better understood. *Both humoral and* ***cell-mediated immunity*** are implicated in the primary processes (the mechanisms that induce kidney injury) and the secondary events (the cascade of the tissue responses activated by initial damage), that mediate renal inflammation and fibrosis. *Nonimmunologic mechanisms* also can propagate ongoing injury. These processes include adaptive hemodynamic and forces, that can cause intraglomerular hypertension and abnormal intravascular stress and strain.

A specific immune response can be generated by both the cellular and humoral immune systems. T-cells for the most part direct the cellular immune response, whereas the antibodies derived from B-cells direct the humoral immune response. Antigen presenting cells (APC) in conjunction with T-cells are essential for the initiation of immune response. *Examples of APC include monocytes, macrophages dendritic cells, and B-cells.* These cells express multi-subunit, major hystocompatibility complex /MHC/ proteins and their cell surfaces.

B-cell can be activated to secrete antibodies by one of two mechanisms. In the first, B cells can bind specific antigen directly via crosslinking Immunoglobulins (Ig) presented on cell surfaces.

Immune mechanisms of glomerular injury

They can be divided in two categories: humoral and cell-mediated. Most of the focus in the past has been on antibody-mediated injury. *Two forms have been established: in situ immune complex disease and circulating immune complex (CIC) disease.* However the antibody deposition is not sufficient to cause renal injury. Cell-mediated tissue injury can occur through the release of cytokine growth factors, or other mediator/midieitъ:/ of inflammation. In vitro results suggest, that inflammatory cells can directly injure the glomerulus, as in pauci GLN. Activation of complement cascade either by the classical or alternative/o:ltъneitiv/ pathway, also play a critical role in glomerular damage.

Humoral immunity. In situ immune complex disease. The binding of antibody (AB) to antigen (AG) localized to within a specific tissue is known as in situ immune complex formation. In situ immune complex disease can occur in two ways: either by antibodies binding to "native" AG or to "planted" AG. **Native antigens** are intrinsic glomerular constituents.

Circulating immune complex disease. In this form of immune complex disease, soluble CIC become passively trapped within the glomerulus, subsequently resulting in renal injury through complement activation, leukocyte infiltration, glomerulus cell proliferation.

CIC can contain endo- and exogenous antigens. Examples of endogenous antigens identified in CIC and implicated in human renal diseases include DNA, thyroglobulin, thyroid antigen, red cell stroma, and tumor neoantigens. *Exogenous antigens are derived primarily from microbes – streptococci and hepatitis viruses B and C.* Fungi and parasites also can serve as exogenous antigen. Soluble foreign proteins (cow, goat), food antigen, chemicals as gold and mercury also act as exogenous antigens.

Cell mediated immunity

Mediators of glomerular immune injury can be divided in two: primary – antibody and T cells; secondary – complement and other inflammatory cells. T-cell mediated mechanisms of immune injury are often independent of antibody deposition.

Classification of chronic glomerulonephritis

There are many kinds of classification of chronic GNF, based on different criteria – etiologic, pathogenetic, clinical. The morphologic (microscopic) criterion is the most preferable in the last three decades. Although the classification-problem remains open, as well more than three classifications exist during the above-mentioned period.

The oldest one is the classification of the Australian nephrolo-gist P. Kincaid-Smith, dated from 1975 year and accepted from WHO in 1977 year.

The second significant classification has been reported in Tokyo on an International congress of nephrology in 1982nd year.

1. GLN with minimal changes.
2. Focal segmental glomerulosclerosis.
3. Mesangial proliferative GLN.
4. Endocapillary GLN.
5. Membranoproliferative GLN, type I and III.
6. Disease of the dense deposits /membranoproliferative GLN type II/.
7. Membranous GLN.
8. Diffuse extra capillary GLN.
9. Diffuse sclerotic GLN.

10. Unclassified GLN.

Bulgarian scientific society of nephrology uses the following “practical” and suitable classification:

1. Idiopathic nephrotic syndrome (INS)-

- Minimal change GLN
- Mesangial proliferative GLN with IgM deposits
- Focal segmental glomerulosclerosis.

2. Membranous GLN .

3. Mesangial proliferative GLN:

а) with Ig G deposits

б) with Ig A deposits.

в) with C3 deposits.

4. Membranoproliferative / mesangial-capillary/ GLN.

Pathomorphologic picture and clinical presentation

Minimal change nephropathy or minimal change disease /MCD/ is a histopathologic form associated always with nephrotic syndrome. Synonyms: lipoid nephrosis, nil disease, disease of the epithelial foot processes.

Hystopathology. On light microscopy – lack of definitive alterations in glomerulus, the cellularity is normal or minimal, the tubular and interstitial structures are too normal. Immunofluorescent staining also shows no change from normal. The most obvious finding is a characteristic fusion of epithelial foot processes. The epithelial cells show swelling and continuous contact with BM. The fenestration of the endothelium and glomerular BM are normal.

Clinical presentation. Although generally thought to be a childhood disease, MCD is presented in both children and adults. The insidious onset of nephrotic syndrome, usually manifested by edema formation is the most common presentation. In preadolescent children 85-95% with INS have MCD. In adolescent and young adults the prevalence of MCD declines to approximately 50% and the male predominance begins to disappear. In the age over 40 years the incidence of MCD is less than 25%, with equal distribution between males and females.

Focal segmental glomerulosclerosis (FSGS)

Pathology. The pathologic diagnosis usually depends on identifying in some glomeruli areas of glomerulosclerosis (focal lesions in part of the glomerular tufts (segmental lesions). In addition fusion or effacement of foot processes is found to some extent in all of the glomeruli, including those unaffected by areas of segmental sclerosis. *Focal areas of IgM and C3 deposition i*solated to the areas of segmental sclerosis are thought to result from entrapment of immunoglobulin and comple-

ment rather than from true immune complex deposits. The remainder of the glomerular tuft typically has some degree of foot process effacement; *they do not have IC deposits*. Interstitial fibrosis also is common finding in biopsies with significant sclerosis.

Clinical features. Most patients present asymptomatic proteinuria or the full nephrotic syndrome. Hypertension is found in 10 to 30% of patients independently of the age. Microscopic hematuria is found in 25 to 75%. Decreased renal function is noted in 20 to 30 %. Daily urinary protein excretion ranges between 1 to 20-30 g. Proteinuria is typically nonselective. Complement level and other serologic tests are normal. Glycosuria, aminoaciduria, phosphaturia and concentrating defect indicated tubular injury as well as glomerular one.

Membranous nephropathy (MN)

MN is histologic diagnosis in 15-25% of adult patients, who have systemic illness and undergo biopsy for heavy proteinuria. Pathology. On light microscopy mesangial regions appear normally. Subepithelial fuchsinophilic deposits are observed, with epithelial projections (spikes), corresponding to the deposition of new basement membrane material. Immunofluorescence microscopy always demonstrates strong granular wall staining for IgG and C3, and not rarely - weaker IgA and IgM staining too. The ultrastructural features allow, the disease to be divided in four stages.

Clinical presentation. The main symptom is heavy proteinuria – in more than 80% of cases, associated with a full demonstration of nephrotic syndrome. In the remaining patients proteinuria is asymptomatic. A minority has microscopic hematuria. Hypertension may be present in minority patients at the start of the disease and certainly develops when renal function becomes limited.

Nephrotic syndrome may be heavy and combined with anorexia, malaise and anasarca. Ascites, pleural, pericardial effusions are les common in adults, than in children.

Membranoproliferative glomerulonephritis /MPGN/

Pathology. Type I is most common. It consists of mesangial expansion owing to increased mesangial cell number and mesangial immune deposits, sometimes imparting a nodular quality. The capillary walls are thickened by extensively mesangial interposition, subendothelial deposits and double contours of the glomerular BM. The degree of glomerular hypercellularity varies from mild to marked, and the severe forms have exaggerated lobularity. By immunofluorescence, the immune deposits usually consist of immunoglobulins and complement components, distributed in a combined granular mesangial pattern and semilinear subendothelial pattern, which outlines the lobular contours. Although IgG and C_3 usually predominate, weaker and more variable staining for IgM, IgA and C1q may also be found.

Type II MPGN is the least common form, known also as “dense deposit disease”. The degree of hypercellularity is highly variable and double contours tend to be less well developed. The define feature is a band-like thickening of the lamina densa of the GBM. By electron microscopy, these consist of distinctive highly electron dense deposits, which replace and transform the lamina densa,

producing smooth, ribbon-like thickenings. Nodular mesangial electron dense deposits are also usually found. By immunofluorescence there is typically positivity for C3 only in a linear double-contoured distribution along the GBM and as a "ring forms" in mesangium.

Type III is relatively uncommon and controversial variant. Two subtypes have been defined.

Clinical features. **The renal manifestation includes nephrotic syndrome and nephritic features, often present in combination.** Other presenting features include asymptomatic hematuria, acute nephritic syndrome, subnephrotic proteinuria, slowly progressive renal insufficiency, and recurrent episodes of gross hematuria. An upper respiratory tract infection, including streptococcal pharyngitis commonly preceded first clinical recognition of the disease.

IgA nephropathy

In 1968 Berger and Hinglais in France described the unique renal immunohistologic features of IgA nephropathy. In subsequent 30 years **it become the most common form of primary GLN in the world and accounts nearly 10% of patients reaching ESRD.**

Pathology. The characteristic light microscopy finding is mesangial enlargement due to proliferation of mesangial cells and or increased mesangial matrix.

IgA is predominant or sole in the mesangium of glomeruli. In the 3/4 of patients a second immunoglobulin - G or M (often both) is detected with staining intensity equal to or less than that for IgA. C_3 staining is usually observed in the same areas.

Electron dense deposits in mesangial and paramesangial areas correspond to the immune deposits. Deposits in subepithelial and intramembranous areas are uncommon. One third of patients exhibit BM abnormalities – focal thinning, splitting and lamination.

Clinical presentation. *Males are affected two to three times more often than females.*

Patients usually present with one of three syndromes. The most distinctive is an episode of macroscopic hematuria coincided with an upper respiratory tract infection. This feature has been labeled "synpharyngitic hematuria". The patient is usually asymptomatic, but sometimes reports malaise, fatigue, or myalgia, loin pain. A few patients develop acute renal dysfunction. Proteinuria is of variable degrees, usually less than 1 g/d. Arterial hypertension is the second syndrome. Hypertension is more common in patients, whose biopsy specimen shows focal sclerosis. Malignant hypertension develops 5% of patients.

Renal biopsy is the method of choice for the establishing of the diagnosis.

Diagnosis

The classic diagnostic tactic includes four steps. First, the physician should to have a maximal volume of information about the main nephritic symptoms, such as edema (time and age of the first advent, severity, evolution, engaged part of body and etc.), arterial hypertension, hematuria (red colour of urine); relationship of complaints with focal infection disease. Second – the data obtained from the detailed physical examination should prove the existing of the true renal

symptoms and syndromes. Third – the laboratory investigations (urinalysis, serum proteins, BUN, creatinine, clearances, microbiologic and immunologic specific probes, sonography, venous X-ray) should present results supporting an immune glomerulopathy. Fourth – the trans-cutaneous renal biopsy is method of choice to assure a histologic verification and a precisely establishment of the type of glomerulonephritis. “No biopsy policy” could be adopted only in cases with biopsy contraindications.

Treatment

Etiologic therapy has little effectiveness. Antibiotic courses with antistreptococcal active agents are not accepted in all cases. The radical eradication of focal infection (tonsillectomy for ex.) is well accepted.

The basic part of the treatment is the pathogenetic therapy. Its aim is to suppress the activating immune system. As immune-suppressive agents are used corticosteroids - in conventional and pulse schemes. Prednison and prednisolon are the preferable drugs for longtime conventional therapy. 6-methyl prednisolon is the preferable agent for pulse therapy.

The other groups of drugs having place as pathogenic agents are: anticoagulants и antiplatelet (heparin, dipyridamole, aspirin, ticllopidin, ibustrin): NSAID (indomethacin, ibuprofen). Plasma separation alone has no application. In more severe forms of CGN it is an excellent method combining the immunosuppressive drugs.