Nephrotic syndrome

Nephrotic syndrome (NS) is defined as a severe disorder of the glomerular basement membrane that leads to increased waste of protein in the urine. [1] NS is characterized by **proteinuria** with subsequent **hypoproteinemia** , **hypoalbuminemia**, **hypercholesterolemia** , and **edema** . It is particularly dangerous due to its possible complications, which are **infections**, **thromboembolic events** , accelerated **atherosclerosis** and **protein malnutrition** . Persistent nephrotic syndrome can progress to **chronic renal failure**.[2] It is a serious clinical syndrome that occurs especially in children, 15 times more often than in adults.[3]In children, the most common cause is so-called **minimal glomerular change disease (MCD)**. Nephrotic syndrome based on MCD is one of the most common glomerulopathies in children (2–3/100,000). [4]

Diagnostic criteria:

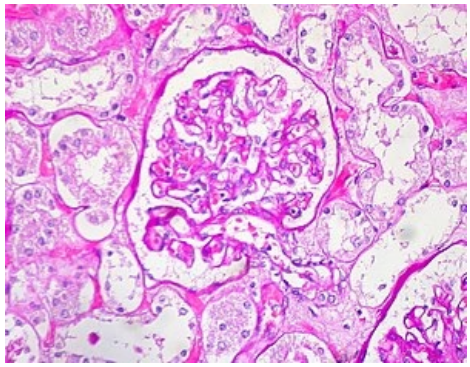
- **proteinuria** > 3,5 g/24 hours[5] (more than 2 g/m^2/day)[5], (50 mg/kg weight)[6];
- **reduced value of plasma albumin** (below 30g/l);
- **peripheral edema**[7];
- hypercholesterolemia > 8 mmol/l[6].

Diagnostic criteria in pediatrics:

- **proteinuria** > 1 g/1 m²/24 hours.;
- **decrease in serum albumin** < 25 g/l.[1]

Etiopatogenesis

Proteinuria is caused by damage to the capillary wall of the glomerulus , which results in increased permeability for protein macromolecules. If protein losses in the urine exceed the proteosynthetic capacity of the liver, hypoproteinemia, hyperlipidemia, and edema develop. [8]


Intact Glomerulus

The capillary wall of the glomerulus consists of:

1. fenestrated endothelium;
2. glomerular basement membrane (irregular network of collagen IV, laminin, entactin molecules) – does not pass proteins with a molecular weight greater than 100–150 kD, its damage (in chronic glomerulonephritis, diabetic nephropathy, AA amyloidosis) leads to non-selective proteinuria;
3. glomerular epithelial cells (podocytes) – the terminal and most selective barrier.[2]

The electrostatic repulsion barrier (sialoprotein macromolecules on the surface of the capillary endothelium, heparan sulfate of the glomerular basement membrane and podocalyxin on the surface of the podocytes) or anion filter ensures charge selectivity (albumin does not pass), its damage leads to selective proteinuria (albuminuria) - typical of nephrotic syndrome with minimal changes .

With milder damage to the filter barrier, macromolecules with a lower molecular weight (albumin) pass through the filter - selective proteinuria , with more extensive damage, substances with a higher molecular weight (e.g. immunoglobulins) pass through the filter in addition to albumin - non-selective proteinuria .

5-20% of NS cases are caused by monogenically inherited diseases. [4] Mutations of plasma membrane proteins (nephrin, podocin) or podocyte cytoskeleton (alpha-actinin) cause congenital or familial nephrotic syndrome .[2]

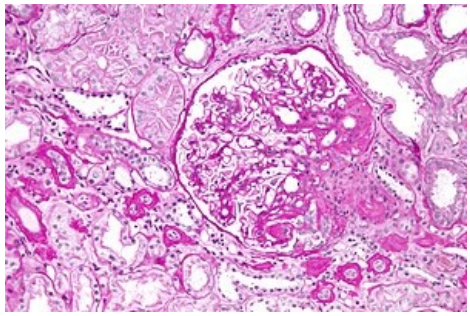
Pathophysiological mechanisms of clinical manifestations:

- increased losses of albumin into the urine lead to hypoalbuminemia and thus a decrease in oncotic pressure, due to which intravascular fluid moves into the interstitium and edema occurs ;
- loss of immunoglobulins into the urine leads to increased susceptibility to infections ;
- the thrombophilic state is caused by reduced intravascular volume with hypocirculation, losses of antithrombin III into the urine, and accompanying thrombocytosis ;
- hyperlipoproteinemia is the result of stimulation of lipoprotein synthesis in the liver during hypoproteinemia or reduced activity of lipoprotein lipase in the plasma due to its loss in the urine.[4]

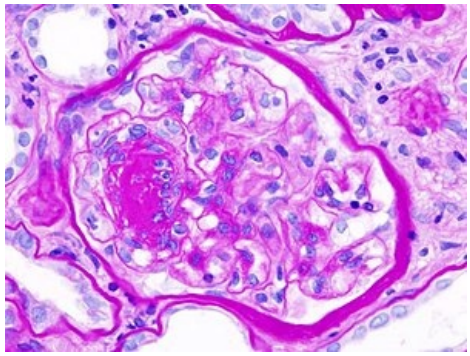
If the intravascular volume is not significantly reduced and there are only minimal changes in the glomerular basement membrane, there is usually a significantly increased glomerular filtration and effective filtration pressure - hyperfiltration. With further protein losses, the volume of circulating blood decreases and glomerular filtration decreases - a paradoxical "normalization" of GF during an adverse course. [1]

Kidney diseases accompanied by nephrotic syndrome

- **Primary glomerulopathy** accompanied by NS:
  - NS with minimal glomerular changes (MCGN) – typically in children from 4 years of age and adolescents; in 95% corticosensitive; [4]
  - focal segmental glomerulosclerosis (FSGS) – corticosensitive in only 30%[4];
  - membranous nephropathy;
  - hereditary nephropathy (congenital nephrotic syndrome of the Finnish type, Denys-Drash syndrome) - in children under 2 years of age.[2]
- **Secondary glomerulopathy** accompanied by NS:
  - diabetic glomerulosclerosis , renal amyloidosis , Alport syndrome , hemolytic uremic syndrome ;
  - lupus nephritis, Henoch-Schönlein purpura , Goodpasture syndrome , rheumatic fever ;
  - congenital toxoplasmosis or CMV, EBV infection, measles , varicella ;
  - vaccinations and some drugs (NSA, D-penicillamine).[2][4]



Focal segmental glomerulosclerosis



Diabetic glomerulosclerosis

Clinical picture

- oliguria, swelling of the upper eyelids and genitals → swelling of the lower limbs, trunk and upper limbs → ascites, hydrothorax;
- weight gain, thirst, reduced diuresis, urine with a high protein content is conspicuously foamy,
- fatigue, alteration of general condition,
- blood pressure mostly normal.[4][1]

Complications of nephrotic syndrome

Infection,

- the cause is a defective immune response,
- most often caused by gram-positive microorganisms (Streptococcus pneumoniae),
- therapy must be started as soon as possible with parenteral antibiotics,

Thromboembolic complications,

- more often venous thrombosis, typically renal vein thrombosis (manifested by sudden pain in the side, impaired renal functions),
- risk of pulmonary embolism – antithrombotic therapy in all patients with renal vein thrombosis,
- prophylaxis – prevention of dehydration, therapy of infections, early mobilization,

Disorders of lipid metabolism,

- increased concentration of total cholesterol in the serum,
- hypertriacylglycerolemia,
- lipiduria with lipid cylinders,
- in patients with longer-term nephrotic syndrome, we start statin therapy ,

Protein malnutrition,

- especially obvious after swelling subsides,
- total albumin is decreased due to urinary losses and increased tubular degradation,
- patients with severe proteinuria tend to be in severe catabolism with a large weight loss that is masked by swelling,
- therefore, an increased protein intake is recommended for nephrotic patients, and a high-protein diet for children.

Diagnostics

- **urine test**:
  - proteinuria > 3,5 g/24 hours (more than2 g/m^2/day)[5]; (50 mg/kg weight)[6]
  - proteinuria/creatinine ratio in the morning urine sample (0.1 g/mmol corresponds to a quantitative proteinuria of 1 g/24 hours) [2],
  - 24-hour urine collection for quantitative proteinuria (examination according to Exton),
  - electrophoretic examination of urine (differentiation of selective and non-selective glomerular proteinuria).[8]

- biochemical **blood test**:

    - hypoproteinemia (normal level is 35–50 g/l)[2],
    - hypoalbuminemia (< 20 g/l)[6],
    - hypercholesterolemia (> 8 mmol/l)[6], hypertriacylglycerolemia[1],
    - natremia is usually normal, it can be hypo due to hemodilution ,
    - hypocalcemia (decreased Ca bound to proteins, but the free fraction is normal),
    - serum creatinine and urea levels are usually normal,
- ELFO serum proteins : hypoalbuminemia and hypogammaglobulinemia, relative increase of α2-globulins,
- the hematocrit is increased, the platelet count is increased,
- high FW[1],
- the levels of some coagulation factors may be increased and vice versa, e.g. antithrombin III leaves in the urine and decreases → all this causes an increased risk of thrombosis [2][4];

- renal biopsy is indicated based on risk factors that suggest a diagnosis other than minimal glomerular change disease. These risk factors include: macroscopic hematuria, age under 12 months and over 15 years, low C3 component of complement, skin exanthema, severe hypertension with microscopic hematuria .[7]
    -
        - with a typical clinical picture in children from 1 to 10 years, biopsy is not indicated;
        - it is recommended for children over 10 years and under 18 months, with macroscopic hematuria , with resistance to glucocorticoids , with a drop in GFR, with hypertension;
        - biopsy findings: minimal glomerular changes are found in 80-90%;
        - in the electron microscope: hypertrophy of podocytes, fusion of their processes, BM has a normal appearance.

Differential diagnosis

- erythrocyturia? → does not occur in NS with minimal changes and in diabetic nephropathy,
- normal blood pressure? → NS with minimal glomerular changes,
- SLE ? → complete an immunological examination (C3, ANA,...),
- susp. AL amyloidosis? → supplement the serum immunoelectrophoretic examination for the presence of paraprotein,
- examination of the selectivity of proteinuria[2].

Therapy

- **symptomatic**:
    - fluid restriction and a diet with salt (sodium) restriction, sufficient intake of calcium and vitamin D ,
    - early mobilization, treatment and prevention of infections, prevention of dehydration and antiplatelet treatment (acetylsalicylic acid), control of arterial blood pressure,[8]

- **casual:**
    - prednisone 60 mg/m 2 /day for 6 weeks (maximum dose is 80 mg/day), in one morning dose or in 3 descending doses,
    - then another 6 weeks of treatment with prednisone at a dose of 40 mg/m 2 every other day (alternative administration),
    - after 12 weeks of treatment prednisone can be discontinued[9].

- léčba otoků (nutná v případě klinických obtíží nebo v případě oligurie),
    - diuretika nebo i. v. albumin + diuretika,
    - diuretika – nejčastěji furosemid, event. furosemid + hydrochlorothiazid, při extrémních otocích + spironolakton,
    - indikace k podání albuminu podle poměru draslíku a sodíku ve vzorku moči – pokud $U_K/U_K + U_{Na} > 0,6$ jde o intravaskulární hypovolemii a je indikováno podání albuminu (1 g/kg v pomalé infuzi, poté i.v. furosemid)[7].

- relaps – objevení proteinurie 100 $g \cdot m^{-2} \cdot den^{-1}$, rychle stoupá, vznikají edémy,
- při neúspěchu kortikoidů – zvažujeme léčbu cytostatiky (cyklofosfamid, chlorambucil – v imunosupresivních dávkách, ne v cytostatických) nebo imunosupresivy (cyklosporin A, azathioprin)[10].

According to the response to steroid treatment, we distinguish between steroid-sensitive NS and steroid-resistant NS. A patient is considered steroid-resistant if they do not achieve remission during the initial 6-week course of corticosteroids. In steroid-sensitive NS, boys are affected twice as often as girls. In steroid-resistant NS, the ratio of both sexes is balanced.[4]

Prognosis

U NS s minimálními změnami je dobrá, v 95 % je citlivý na kortikoidy. NS s fokálně segmentální sklerózou je často kortikorezistentní a u poloviny pacientů se do 10 let vyvine chronické renální selhání.

Links

Related articles

- Nephritic syndrome
- Glomerulonephritis
- Alport syndrome
- Glomerulopathy: Glomerulopatie projevující se nefrotickým syndromem
- Diabetická glomeruloskleróza (preparát)

External links

- prof. MUDr. Merta, CSc.: Nefrotický syndrom, *Urologie pro praxi (2010)* (http://www.urologiepropraxi.cz/pdfs/uro/2010/03/06.pdf)
- MUDr. Geier, PhD.: Léčba steroid-senzitivního nefrotického syndromu u dětí, *Pediatrie pro praxi (2010)* (https://www.pediatriepropraxi.cz//pdfs/ped/2010/05/04.pdf)
- prof. MUDr. Tesař, DrSc.: Nefrotický syndrom, *Medicína pro praxi (2008)* (http://www.solen.cz/pdfs/med/2008/02/04.pdf)
- MUDr. Geier: Nefrotický syndrom, *Pediatrie pro praxi (2001)* (http://www.solen.cz/pdfs/ped/2001/03/05.pdf)
- Česká lékařská společnost: Doporučené postupy (http://www.cls.cz/seznam-doporucenych-postupu)

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10. BENEŠ, Jiří. *Studijní materiály* [online]. ©2007. [cit. 2010-04]. <http://www.jirben.wz.cz/>.

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