Nephrotic Syndrome

Nephritic vs nephrotic syndromes (recap, progression likelihood):

Nephrotic syndrome (NS) is defined as a severe disorder of the glomerular basement membrane that leads to increased urinary protein waste.[1] NS is characterized by proteinuria followed by hypoproteinemia, hypoalbuminemia, hypercholesterolemia and edema. It is particularly dangerous because of its potential complications, which are infections, thromboembolic events, accelerated atherosclerosis and protein malnutrition. Persistent nephrotic syndrome may progress to chronic kidney disease. [2] JIt is a severe clinical condition that occurs primarily in children, 15 times more frequently than in adults.[3] In children, the most common cause is the so-called **minimal change disease** glomerular disease (MCD). Nephrotic syndrome due to MCD is one of the most common glomerulopathies in children (2-3/100,000). [4]

Nephrotic syndrome (glomerulonephrosis; glomerulosclerosis):

Diagnostic criteria:

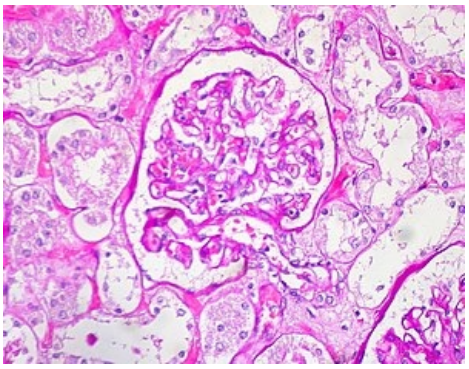
- **proteinuria** > 3.5 g/24 hours[5] (více než 2 g/m^2/den)[5], (50 mg/kg hmotnosti)[6];
- **decreased plasma albuminu** (below 30g/l);
- **peripheral edemas**[7];
- hypercholesterolemia > 8 mmol/l[6].

Diagnostic criteria in pediatrics:

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

Etiopathogenesis

Proteinuria is caused by damage to the capillary wall of the glomerulus, resulting in increased permeability to protein macromolecules. If protein loss to the urine exceeds 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 basal membrane (irregular network of collagen IV, laminin, entactin molecules) - it does not allow proteins with 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 capillary endothelium, heparan sulfate of the glomerular basement membrane and podocalyxin on the surface of podocytes) or anion filter provides 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 of lower molecular weight (albumin) pass through the filter - ***selective proteinuria***, with more extensive damage, substances of 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 the podocyte cytoskeleton (alpha-actinin) cause **congenital** or **familial nephrotic syndrome**.[2]

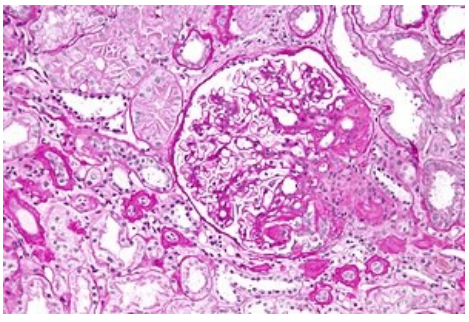
Pathophysiological mechanisms of clinical manifestations:

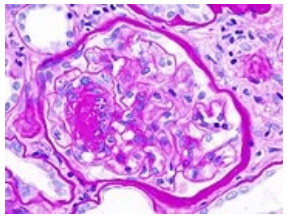
- increased albumin loss into the urine leads to hypoalbuminemia, resulting in a decrease in oncotic pressure, which causes intravascular fluid to move into the interstitium, resulting in **edemas**;
- loss of immunoglobulins into the urine leads to increased **susceptibility to infection**;
- **thrombophilic state'** is caused by decreased intravascular volume with hypocirculation, loss of antithrombin III into the urine and accompanying thrombocytosis;
- **hyperlipoproteinemia** *is the consequence of stimulation of lipoprotein synthesis in the liver in hypoproteinemia or decreased plasma lipoprotein lipase activity due to its loss into the urine.*[4]

Unless the intravascular volume is significantly reduced and there are only minimal changes in the glomerular basement membrane, there is usually a significant increase in glomerular filtration and effective filtration pressure - hyperfiltration. With further protein loss, the circulating blood volume decreases and glomerular fitration decreases - a paradoxical "normalization" of GF in an adverse course.[1]

Kidney disease accompanied by nephrotic syndrome

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


Focal segmental glomerulosclerosis


Diabetic glomerulosclerosis

Clinical picture

- oliguria, **swelling of the upper eyelids** and genital area → swelling of the lower extremities, trunk and upper extremities → ascites, hydrothorax;
- wax gain, thirst, decreased diuresis, urine with high protein content foams prominently,
- fatigue, alteration of general condition,
- blood pressure mostly normal.[4][1]

Complications of nephrotic syndrome

Infection,

- caused by a defective immune response,
- caused most commonly by gram-positive microorganisms (*Streptococcus pneumoniae*),
- therapy should be initiated as soon as possible with parenteral antibiotics,

Thromboembolic complications,

- more often venous thrombosis, typically renal vein thrombosis (manifested by sudden onset of flank pain, impaired renal function),
- risk of pulmonary embolism - antithrombotic therapy in all patients with renal vein thrombosis,
- prophylaxis - prevention of dehydration, infection therapy, early mobilisation,

Lipid metabolism disorders,

elevated serum total cholesterol concentration, hypertriacylglycerolaemia,

- lipiduria with lipid cylinders,
- in patients with prolonged nephrotic syndrome, initiate statin therapy,

Protein malnutrition,

especially after the swelling subsides,

- total albumin is reduced due to urinary losses and increased tubular degradation,
- patients with severe proteinuria tend to be in severe catabolism with large weight loss masked by edema,
- increased protein intake is therefore recommended in nephrotic patients, and a high-protein diet in children.

Diagnosis

- **urinalysis**:
  - proteinuria > 3.5 g/24 hours (more than 2 g/m^2/day)[5]; (50 mg/kg of weight)[6]
  - proteinuria/creatinine ratio in 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 (Exton assay),
  - electrophoretic urinalysis (differentiating selective and non-selective glomerular proteinuria)[8]

- biochemical **blood test**:
  - hypoproteinemia (normal level is 35-50 g/L)[2],
  - hypoalbuminemia (< 20 g/l)[6],
  - hypercholesterolaemia (> 8 mmol/l)[6], hypertriacylglycerolaemia[1],
  - natremia is mostly normal, may be hypo due to hemodilution,
  - hypocalcemia (decreased protein-bound Ca but free fraction is normal),
  - serum creatinine and urea levels are usually normal,
- ELFO of serum proteins: hypoalbuminemia and hypogamaglobulinemia, relative increase in α2-globulins,
- hematocrit is elevated, platelet count is elevated,
- high FW[1],
- levels of some coagulation factors may be elevated and conversely, e.g. antithrombin III goes into the urine and decreases → all of these cause an increased risk of thrombosis[2][4];

- **renal biopsy** is indicated based on risk factors that are indicative of a diagnosis other than minimal glomerular change disease. These risk factors include: macroscopic hematuria, age below 12 months and above 15 years, low C3 complement component, skin exanthema, severe hypertension with microscopic hematuria.[7];

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  - in the typical clinical picture in children aged 1 to 10 years, biopsy is not indicated;
  - recommended in children over 10 years and under 18 months, in macroscopic hematuria, in glucocorticoid resistance, in decreased GFR, in hypertension;
  - bioptic findings: minimal glomerular changes are found in 80-90%;
  - electron microscopy: hypertrophy of podocytes, confluence of their processes, BM has normal appearance.

Differential diagnosis

- erythrocyturia? → absent in NS with minimal changes and in diabetic nephropathy,
- normal blood pressure? → NS with minimal glomerular changes,
- SLE? → complete immunological examination (C3, ANA,...),
- susp. AL amyloidosis? → complete immunoelectrophoretic serum testing for paraprotein,
- proteinuria selectivity test[2].

Therapy

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

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

- treatment of oedema (necessary in case of clinical difficulties or in case of oliguria),
  - diuretics or i.v. albumin + diuretics,
  - diuretics - most commonly furosemide, possibly furosemide + hydrochlorothiazide, in extreme edema + spironolactone,
  - indications for albumin administration according to the potassium-sodium ratio in the urine sample - if $U_K/U_K + U_{Na} > 0.6$ it is intravascular hypovolemia and albumin administration is indicated (1 g/kg in a slow infusion, then i.v. furosemide)[7].

- relapses-appearance of proteinuria 100 g-m^{-2}-$days^{-1}$, rises rapidly, edema develops,
- if corticosteroids fail - consider treatment with cytostatics (cyclophosphamide, chlorambucil - in immunosuppressive doses, not cytostatics) or immunosuppressants (cyclosporine A, azathioprine)[10].

According to the response to steroid treatment, we distinguish steroid-sensitive NS and steroid-resistant NS. A patient is considered steroid-resistant if he/she does not achieve remission during the initial 6-week corticosteroid treatment. In steroid-sensitive NS, boys are affected 2 times more often than girls. In steroid-resistant NS, the sex ratio is equal.[4]

Prognosis

The prognosis for NS with minimal changes is good, with 95% being sensitive to corticosteroids. NS with focal segmental sclerosis is often corticosteroid resistant and half of patients develop chronic renal failure within 10 years.

Links

Related articles

- Nephritic syndrome
- Glomerulonephritis
- Alport's syndrome
- Glomerulopathy: Glomerulopathy presenting as nephrotic syndrome
- Diabetic glomerulosclerosis (preparation)

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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2. TESAŘ, Vladimír. Nefrotický syndrom - patogeneze, diagnostika, komplikace, léčba. *Pediatrie pro praxi* [online]. 2008, y. 9, p. 62-64, Available from <https://www.pediatriepropraxi.cz/>. ISSN 1803-5264.
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5. Souček M. a kol. Vnitřní lékařství. Praha Grada Publishing 2011, s. 425, ISBN 978-80-247-2110-1
6. ČEŠKA, Richard, Tomáš ŠTULC, Vladimír TESAŘ a Milan LUKÁŠ. *Interna*. 2., aktualizované vydání. V Praze: Stanislav Juhaňák - Triton, 2015. ISBN 978-80-7387-885-6

7. https://www.pediatriepropraxi.cz//pdfs/ped/2010/05/04.pdf
8. MERTA, Miroslav. Nefrotický syndrom. *Urologie pro praxi* [online]. 2010, y. 11, no. 3, p. 140-143, Available from <http://www.urologiepropraxi.cz/pdfs/uro/2010/03/06.pdf>.
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10. BENEŠ, Jiří. *Studijní materiály* [online]. ©2007. [cit. 2010-04]. <http://www.jirben.wz.cz/>.

Source

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

Used literature

- HRODEK, Otto – VAVŘINEC, Jan, et al. *Pediatrie.* 1. edition. Praha : Galén, 2002. ISBN 80-7262-178-5.

- ŠAŠINKA, Miroslav – ŠAGÁT, Tibor – KOVÁCS, László, et al. *Pediatria.* 2. edition. Bratislava : Herba, 2007. ISBN 978-80-89171-49-1.