PATHOPHYSIOLOGY OF KIDNEY

F. Vožeh

SCHEME OF THE LECTURE

I. INTRODUCTION

II. CATEGORIZATION OF RENAL DISEASES

III. ACUTE RENAL FAILURE

IV. CHRONIC RENAL FAILURE

V. GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME

VI. RENAL STONES

VII. SUBSTITUTION OF RENAL FUNCTION

I. INTRODUCTION

The kidneys are the most important organs of excretion with significant impact on homeostasis of the organism

- **patients with renal disease have early typical abnormalities of urine volume or composition**
- **later manifest symptoms of lost renal function: edema, fluid overload, electrolyte abnormalities**
- **depending on the nature of the renal disease, they may progress (rapidly or slowly) to chronic stage with typical complications**
- **pain is not a typical symptom (except renal stones)**
- **many systemic diseases may be manifested in the kidney and the insufficient renal functions have impact on many organs and systems of the body**
- **without right treatment, renal disease may result in loss of sufficient kidney function to be incompatible with life**

Morphology and function of the kidney cortex and medulla

Cortex

- **represents the environment which is isosmotic with blood plasma**
- **it contains glomeruli, proximal and distal tubules.**

3 sorts of glomeruli (nephrons)

- **1) superficial – external cortical layers**
- **2) intermedial – medial cortical layers**
- **3) juxtamedullar – cortex – medulla border**

Medulla

- **creates the inner part of the kidney, where in normal conditions osmolarity increases in direction from the cortex to the renal pelvis**

  contains direct parts of the proximal and distal tubules, the Henley loops and the collecting ducts

The kidney blood circulation

(glomerular afferent arterioles, capillaries and efferent arterioles, vasa recta, peritubular circulation)

Function of the individual parts of the nephron

- **Glomerulus -** function mainly dependent on renal blood flow and filtration pressure
- **Proximal tubule** - active and passive reabsorption, tubular excretion, obligate reabsorption of water (80-87% GF)
- **Henle's loop** - osmotic stratification of the kidney marrow
- **Distal tubule** - tubular resorption and excretion facultative reabsorption of water (12-19% GF)
  Collecting duct - finishing urine osmolarity

Examination of the kidney function

clearance (endogenous creatinine or inulin - 120 ml/min - glomerular filtration) PAH 600 ml / min. - RPF / 1 min.

clearance of inulin / PAH clearance = 120/600 x 100 = 20% which is an FF (filtration fraction)

concentration experiment (1028 - 1035 g/l, i.e. 1400 mOsm/l)

dilution experiment (1002 - 1003 g/l, i.e. below 350 mOsm/l)

Newly, the kidney concentration ability is determined by ADH test (administration of 2 drops into the nose in the morning after urination and then measuring the concentration of urine).

Results are dependent on age: under 20 years the normal concentration is about 970 mOsm/l (1028 g/l); below 50 years, about 850 mOsm/l (1022 g/l)

hyposthenuria- kidneys unable to concentrate normally urine

isosthenuria - kidneys excrete urine of the same concentration as blood plasma (about 350 mOsm/l = 1010 g/l, therefore it is isotonic)

Regulation of the kidney function

- **Mechanisms physical (countercurrent multipliere system)**

- **<u>Mechanisms neural</u> (mainly sympathetic innervation by the renal nerves as one of influences on renin release which regulates the kidney blood flow)**

- **<u>Mechanisms hormonal</u> (dealing mainly with tubular processes) where are acting first of all:**

  neurohypophysis (ADH)
  suprarenal glands (aldosterone)
  parathyroid gland (parathormone)
  system renin - angiotensin

Manifestations of the kidney function disorders

- **Acid – base imbalance, water and electrolyte abnormalities**
- **Uremia as a result of inadequate excretion of BUN (blood urea nitrogen)**
- **Increased intravascular volume, hypertension and congestive heart failure, peripheral edema**

II. CATEGORIZATION OF RENAL DISEASES

According to:

- **the site of the lesion (glomeruli, tubules, interstitium)**
- **etiological factors (immunologic, metabolic, infectious, toxic, infiltrative, hemodynamic)**

General characteristics of pathogenetic mechanisms to the kidney structure

- **renal medulla – low oxygen tension environment (more susceptible to ischemia)**
- **glomerulus – the initial filter of blood and therefore a prominent site for injury from immune complex deposition and complement fixation**
- **hemodynamic factors – regulation of the blood flow and so influencing renal function (GF, relationship to hypoxic injury)**

Categorization with the respect to the site and the cause of renal disease

Causes:

- **Prerenal** – common feature is inadequate blood flow to the kidney

- **Renal** – direct damage to the nephron

- **Postrenal** – related to urinary tract obstruction (kidney stones, tumors, strictures, prostatic hypertrophy etc.)

III. ACUTE RENAL FAILURE

The rapid deterioration of renal function resulting in accumulation in the blood nitrogenous wastes that would normally be excreted in the urine.

- **oliguria**
- **uremia (in severe cases)**
- **typical laboratory findings in the blood and urine**

Etiology

- all 3 types of disorders

Pathogenesis

- **tubular theory** (occlusion of tubular lumen with cellular debris which forms casts that increases intratubular pressure and decreases filtration pressure)
- **vascular theory** (decreased renal perfusion pressure from the combination of vas afferent constriction and vas efferent dilatation reduces glomerular filtration pressure)

Clinical manifestations

- **reversible stage (prerenal azotemia)** (the urine is maximally concentrated – up to 1500 mOsm/l)

- **irreversible stage (tubular necrosis)** (the ability to generate a concentrated urine is lost and urine osmolality is less than 350 mOsm/l) **isostenuria** (identical osmolarity with blood plasma)

VI. CHRONIC RENAL FAILURE (CHRF)

The long-term insufficiency of progressive nature that causes the additional deterioration of others tissues and organs as:

- **osteodystrophy**
- **neuropathy**
- **bilateral small kidneys shown by abdominal x-ray or ultrasound,**
- **anemia**

Long-term asymptomatic state (because of the enormous functional reserve of the kidneys

– **up to 50% of nephrons can be lost without any evidence of functional impairment –** advantage for donors of the organ for transplantation.

When glom. filtration is reduced to the 30-50% range, some degree of azotemia is observed. Only below 20% of normal, renal capacity excretory capacity is insufficient to prevent uremia).

Increased perfusion of residual nephrons helping to maintain adequate glomerular filtration leads to their overload and sclerotization. This leads to further reduction of functioning nephrons and represents a mechanism of progression of chronic renal failure.

Etiology

1) diabetes mellitus
2) hypertension
3) glomerulonephritis
4) polycystic kidney disease
5) other, unknown

CHARACTERISTICS of CHRF

I. **CHRF results in irreversible loss of nephrons**

II. **<u>As a result of a greater functional burden</u> the surviving nephrons suffer from higher filtration pressure (compensatory hyperfiltration) and this "hypertension" at the level of individual nephrons predisposes them to fibrosis and scaring (glomerular sclerosis) and to further destruction.**

III. **It results in increased loss of nephrons with progression to uremia.**

IV. **Owing to big functional reserve of the kidney, up to 50 % of nephrons can be lost without any functional impairment (important for healthy donors of one kidney for transplantation)**

V. **When GFR is reduced to the 30 – 50 % of normal state, some degree of azotemia is observed.**

VI. **Nevertheless, patients may be asymptomatic because a new „steady state“ is achieved.**

VII. **Hyperfiltration as well as further loss of nephrons continue and the accelerated evolution to end stage CHRF is in progress.**

VIII. **Because of little functional reserve the patients with this GFR level can easily become uremic with any added stress (eg. infection, obstruction dehydration, nephrotoxic medicaments etc.)**

IX. **When GFR decreases below approximately 20 % of normal, renal excretory capacity is unable to prevent the development of typical uremia.**

The pathogenesis of uremia in CHRF is derived from combination of toxic effects:

1) retained products normally excreted by the kidneys
2) normal products (e.g. hormones present in increased amounts in this situation)
3) loss of normal products of the kidney (erythropoietin, insulinases)

Increased level of intracellular sodium and water and decreased intracellular potassium have impact on fluid metabolism alteration of enzyme and transport systems function.

The effect of uremia on metabolism

1. A decrease in basal body temperature.
2. Slowed glucose metabolism (partly because of increased peripheral resistance to insulin action)
3. Depressed lipoprotein lipase activity (accelerated atherosclerosis).
4. Immunosuppressive effect
5. Uremic coma

Clinical and pathophysiological consequences of chronic renal failure

A. Sodium balance and body fluid volume status

B. Potassium balance disorder - hyperkalemia

C. Metabolic acidosis

D. Mineral and bone disorders

E. Cardiovascular and pulmonary abnormalities

F. Hematologic abnormalities

G. Neuromuscular abnormalities

H. Gastrointestinal abnormalities

I. Endocrine and metabolic abnormalities

J. Dermatologic abnormalities

V. GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME

Characteristics:
disorders with structural alterations of the glomerulus and with the following findings:
- hematuria
- proteinuria
- reduced GFR
- hypertension
- edema

Disorders are divided into five categories:
1) Acute glomerulonephritis
2) Rapidly progressive glomerulonephritis
3) Chronic glomerulonephritis
4) Nephrotic sy. (proteinuria, hypoalbuminemia, hyperlipidemia, edema)
5) Asymptomatic urinary abnormalities

Characteristics and etiology

1. Acute glomerulonephritis - an abrupt onset of hematuria and proteinuria with reduced GFR and renal salt and water retention which occurs most typically as a consequence of infectious diseases (pharyngeal or cutanerous) with certain „nephritogenic“ strains of group A beta-hemolytic streptococci. **Patients completely recover.**

2. Rapidly progressive glomerulonephritis – state, when recovery from the acute disorder does not occur and worsening renal function results in irreversible and complete renal failure which display all of the feature for chronic renal failure.

3. Chronic glomerulonephritis – situation in which renal impairment following acute glomerulonephritis progresses slowly (over a period of years) into chronic renal failure.

4. Nephrotic syndrome - typical of marked proteinuria, particularly albuminuria (24-hour urine protein excretion > 3.5g), hypalbuminemia, edema, hyperlipidemia and fat bodies in the urine.

Chronic glomerulonephritis and nephrotic sy are of unclear origin nevertheless, in patients with ch. g. the progressive renal deterioration proceeds slowly but inexorably, resulting in chronic renal failure as many as 20 years after initial urine abnormalities.

5. Asymptomatic urinary abnormalities - states of hematuria and proteinuria (in amounts below those seen in nephrotic sy) but no functional abnormalities associated with reduced GFR, edema, or hypertension. The development of this type of chronic renal failure proceeds slowly over decades.

The most common cause of asymptomatic urinary abnormalities is IgA nephropathy, a poorly understood immune complexes disease characterized by diffuse mesangial deposition**.**

Pathogenesis

The different forms of glomerulonephritis and nephrotic syndrome probably represent differences in the nature, extent, and specific cause of immune-mediated renal damage with a number of specific cytokines which play an important role in these processes.

Clinical manifestations

Damage to the glomerular capillaries results in:

- hematuria a proteinuria
- a fall of GF with edema and hypertension as a consequence of fluid and salt overload (in case of excess consumption)
- a transient fall in serum complement (as a result of immune complex and complement deposition in the glomerulus)
- an elevation of titer of antibody to streptococcal antigens is observed in cases associated with group A beta-hemolytic streptococcal infections.

- patients with the nephrotic syndrome have profoundly decreased plasma oncotic pressures due to the loss of serum proteins in the urine. Despite activation of renin – angiotensin – aldosterone and sympathetic nervous system, higher secretion of vasopressin (ADH), there is altered renal response to atrial natriuretic peptide

- for the reasons such patients may develop signs of intravascular volume depletion, including syncope, shock, and acute renal failure

- hyperlipidemia associated with nephrotic syndrome appears to be a result of decreased plasma oncotic pressure, which stimulates hepatic VLDL synthesis and secretion.

Loss of other plasma proteins besides albumin in nephrotic syndrome may present as:

1) A defect in bacterial opsonization and thus increased susceptibility to infections (e.g., due to loss of IgG).

2) Hypercoagulability (e.g., due to antithrombin III deficiency, reduced levels of protein C an protein S, hyperfibrinogenemia and hyperlipidemia.

3) Vitamin D deficiency and secondary hypoparathyroidism (due to loss of vitamin D binding proteins).

4) Alerted thyroid function tests without any true thyroid abnormality (due to reduced levels of thyroxine-binding globulin).

VI. RENAL STONES

Etiology

1. **idiopathic hypercalciuria**, with hyperuricosuria and hyperparathyroidism
2. **uric acid stones because of hyperuricosuria** – typically in patients with gout.
3. **defective transport of aminoacids** is typical in cystinuria and stones of the cystine origin
4. **further stones are created together by salts** as: phosphates, from magnesium, ammonium with participation of infection (proteus)

Pathogenesis

- renal stones – result of disorder in dynamic of solubility of various substances in urine with their following precipitation
- creation of renal stones - dependent on diet, urine pH and physical activity, which can disturb solubility balance of hypersaturated solutions and lead to precipitation of stones

Clinical manifestations:

- patients suffer from **hematuria, pain and sometimes fever**

- Further symptoms depend on presence of other kidney diseases, where the stone is fixed and also if the second kidney is in order.

Presence of renal stones can block the production of urine!

Complications

- **hydronephrosis**
- **infection**
- **renal damage**
- **hypertension**

Prevention

- **diet, follow the drinking regime (but not mineral water), physical exeroise,**
- **avoiding dehydration**

VII. SUBSTITUTION OF RENAL FUNCTION

The aim is to help people to survive the kidney failure

The most frequently used methods:

1) Hemodialysis

2) Peritoneal dialysis

At units of intensive care the continual clearing methods are used in the treatment of severe health problems.

1. Hemodialysis

For the firs time used „artificial kidney“ in 1943 by J. W. Kolf in Netherlands, in our country then in 1955.

- two main principles are used in this method: **diffusion** and **filtration** through a semipermeable membrane.

- the speed of water, salt, electrolytes and waste products´ passage by means of the diffusion depends on:

a) concentration gradient between solutions separated by the membrane,
b) molecular weight of the substances transported,
c) permeability of the membrane, i.e. its thickness and size of its pores.

A base of the ultrafiltration is a passage of a solvent (water) through the membrane according to the principle of pressure difference on either sides of the membrane when the solvent takes along the substances dissolved in it.

The most important part of the device is a dialyzer where the cleaning of blood takes place. The dialyzer consists of 2 parts separated by a semipermeable membrane

- blood flows through the first part,
- the dialysis fluid through the second one.

The direction of flow of both fluids is led in opposite directions.

Dialysis membranes originally based on cellulose are substituted recently by more biocompatible synthetic ones. Because hemodialysis represents an extracorporal circuit, the anticoagulation therapy has to be used. A special procedure (without heparinisation) is used in patients with hemocoagulation diseases.

Because of the long-term and repeated treatment, there is necessary to provide a vascullar access (temporary or permanent) using mainly: v. subclavia, jugularis, femoralis, a. radialis, v. cephalica).

Indications for HD

1) **acute renal failure of various etiology** (incl. sepsis, polytrauma with multiple organ system failure), when a continual dialysis is often used.

2) **regular dialysis** – all people suffered from chronic renal failure unable to survive without HD.

Complications in the course of hemodialysis

a) hypotension – due to not optimally set ultrafiltration

b) muscle cramps – due to ion dysbalance

c) hypo- or hypernatremia, hypokalemia, hypocalcemia

d) disequilibrium sy – CNS due to a prompt decrease of urea in blood and slow in the cerebrospinal fluid (headache, confusion, cramps up to the unconscious).

e) hemorrhage – in various places

f) chest- and back pain – due to allergic reaction (against dialysis membrane), sometimes typical pain of anginous character as a result of decreased Hb, hypotension etc.

g) arrhythmias – due to rapid electrolyte changes

h) fever – allergy, pyrogens in the dialysis fluid or infection of vascular cannula etc.

Complications in the course of longer dialysis therapy

as the sum of:

- renal failure (hypertension, anemia, renal osteopathy)
- dialysis (dialysation amyloidosis, aluminium intoxication).

Cardiovascular complications

- **ischemic heart disease including MI**– in young patients (15 – 35 year of age) 100x more frequent compared to healthy people
- over 55 - 10x more frequent, heart failure, cerebrovascular events),
- **joint and bone complications** (joint amyloidosis, osteomalacia)
- **infection** (vascular accesses, uroinfection, bronchopneumonia)

The definite solution to these problems is the kidney transplantation

2. Peritoneal dialysis

Utilizes specially prepared solutions (1-3 liters) introduced into the peritoneal cavity via a special catheter. The dialysate is hyperosmolar to the serum (in dependence on the concentration of glucose solution used for preparation of it). So it induces solute and fluid exchange between the peritoneal capillary blood and dialysis solution in peritoneal cavity, across the semipermeable peritoneal membrane.

Various procedures:

- **continual (**dialysate in the perit. cavity is permanently);
- **intermittent** (dialysate in the perit. cavity is irregularly)

Advantages:

- movability during therapy
- home therapy
- cheaper than HD
- more gentle to residual renal function than HD
- no bleeding complications

Disadvantages and complications of peritoneal dialysis:

- inadequate is dialysis in obese people without residual renal functions
- peritonitis
- catheter tunnel infections
- presence of ATB in dialysate (in the past)
- malnutrition (loss of appetite from glucose absorption) etc.

Hemoperfusion

Removal of solutes by adsorption to charcoal or resin, primarily for treatment of acute poisoning; can be combined with hemodialysis.

Plasmapheresis

Plasmapheresis is a blood purification procedure used to treat several autoimmune diseases. It is also known as therapeutic plasma exchange.

The basic procedure consists of:

- removal of blood
- separation of blood cells from plasma, and
- return of these blood cells to the body's circulation, diluted with fresh plasma or a substitute

Because of concerns over viral infection and allergic reaction, fresh plasma is not routinely used. Instead, the most common substitute is saline solution with sterilized human albumin protein. During the course of a single session, two to three liters of plasma is removed and replaced.

The end