Pyelonephritis.doc

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Зміст
**Pyelonephritis (PEN).** This is microbial inflammatory kidney disease with lesion of calyces, pelvises and later interstitial tissue of parenchyma and tubules. According to different authors PEN is revealed in 2-3% of grown-up persons; the disease begins in early childhood in 50-70% of cases.

Etiology. Bacteria which caused PEN are, as a rule, intestinal commensals, that are microbes living in the intestine of healthy persons: E.coli, Proteus, Enterococci, Klebsiellas, more rarely St.aureus or epidermidis, Pseudomonas aeruginosa.

There are particular varieties of E.coli and Proteus in urine: E.coli with antigens 01, 02, 04, 06, 075 and K-1, K-2 antigens; Proteus rettregi or mirabilis. The change of bacterial strain or even species of pathogens is seen in the course of disease; not rarely recurrent exacerbations are caused by mixed bacterial flora.

Absence of bacteriuria in patients with pyelonephritis after antibacterial therapy does not testify to the fact that bacteria do not play the main role in pathogenesis of subsequent kidney lesion. It has been proved that bacterial antigens (lipopolysaccharides) are revealed in kidneys of sick persons 5-6 months after the disease exacerbation in absence of bacteriuria during 2-5 months. Prolonged circulation of amorphous bacterial antigen in the kidneys of patients with pyelonephritis may create conditions for more easy reinfection than in healthy children. L-forms of bacteria (so called protoplasts, that is bacteria without cell membrane) play an important role in pathogenesis of chronic pyelonephritis. Protoplasts perish in hypotonic medium of organism tissues, but in hypertonic medium of renal medulla or in conditions of intraepithelium parasitism they may survive and turn into vegetative form, e.g. under the influence of intercurrent infections.

Viruses, Mycoplasms, Chlamydiases play the role in persistence of bacterial antigens in the kidneys.

Chronic renal diseases (first of all PEN) in the family, especially in the mother (particularly PEN during pregnancy) are the most important predisposing factors for development of PEN.

Pathogenesis. According to contemporary investigations, there are disorders of urodynamics in great majority of patients with PEN. It is considered that disorders of urodynamics precede the appearance of PEN which can occur only in their presence. Urogenic (ascendant) way of contamination is the main one for the infection to get into pelvises, tubules and interstitium. The doctrine about reflux (backward flow) explains how the microbes get into the kidney when usual urine flow is from top to bottom.

Reflux are pathologic conditions appeared as a result of anatomical defects, which prevent urine flow, or disorders of nervous regulation of muscular tonus of different parts of the urinary system. Vesicourethral (VUR) and pelviorenal (PRR) refluxes are known. The latter is divided in pelvio-tubular and forinal.

There are 5 grades of VUR according to International classification: grade I - contrast goes only into ureters during cys-tography; grade II - contrast fills unchanged ureter, pelvis and calyces; grade III - mild or moderate distortion and/or curve of ureter, moderate distortion of pelvis, smoothed picture of calyces; IV grade - marked distortion and/or curve of ureter, pelvis, calyces, total disappearance of acute angles in the calyx picture, but preservation of papillary picture in the majority of calyces; V grade - strongly pronounced distortion and curve of ureter (megaureter) and calyces, loss of papillary picture of calyces.

**VUR may be stipulated by:**

1. Anatomical defects (diverticulum or doubling of urethra; short intramuscular part of urethra, that is part in a wall of urinary bladder); muscular and nervous pathology in the region of Lieto triangle (triangle among foramens of ureters and urethra) etc.

2. **Cystitis.**

3. Disorders of nervous regulation of muscular wall and bladder sphincters (so-called neurogenic bladder - NB).

The term "neurogenic bladder" unites different forms of disorders of reservoir and evacuator urinary bladder’s functions, which develop because of nervous system lesions at different levels (from cerebral cortex to intramural apparatus). The most severe forms of NB with VUR of III-V degree are seen in myelodysplasias (according to some authors 1/3-1/2 of such patients have myelomeningocele), injuries (including birth spinal injury), tumors, inflammatory-degenerative diseases of the spinal cord.

According to contemporary theories the independent pathology - reflux nephropathy - exists, which is prerequisite not only for development of PEN, but arterial hypertension as well. It is characterized by gross renal cortical scarring predominantly at both poles. The scars are usually sharply demarcated from the adjacent unscarred parenchyma. The underlying calyces show clubbing and loose their normal concave shape, which is due to papillary distortion and retraction following scar contraction. Such scarring occurs early in life while the kidney is still growing and formation of fresh scars after the age of 5 years is uncommon.

VUR of grade I may disappear in 89% of cases, grade II - in 86%, III - in 83%, IV-V - in 41%. Severe fetal VUR may lead to great loss of renal parenchyma and renal insufficiency even in the newborn. In newborns VUR is invariably complicated by infection and further PEN.

The lesions of interstitial renal tissue are the second condition for appearance of PEN (the first one is...
disorder of urodynamics). Viral and Mycoplasma infections, drug lesions (e.g. hypervitaminosis D), dysmetabolic nephropathies may be their cause. As a result of the above mentioned obstructive disorders, which form VUR, lesions of renal interstitial tissue, so called "locus minoris resistaentiae", are formed in the kidneys, and PEN may appear on the ground of reduced organism reactivity.

Intercurrent diseases of the genital organs (vulvitis, vulvovaginitis), dental caries, chronic cholecystitis, colitis, tonsillitis may be the cause of bacteriuria and bacteriemia as well as pathology of the gastrointestinal tract.

Autoallergy plays the role in pathogenesis of chronic PEN. Detection of antibodies to Tamm-Hoursefield protein in the blood, development of hypersensitivity reaction of delayed type indicates it.

Thus, the following factors play the role in pathogenesis of PEN:

1. disorders of urodynamics;
2. bacteriuria;
3. preceding lesions of interstitial renal tissue;
4. disorders of the organism reactivity.

The role of hereditary factors in pathogenesis of chronic PEN is obvious. In particular, chronic PEN may be the manifestation of hereditary disorders of metabolism and tubulopathies, hereditary immune defects, fetopathies which lead to renal dysembryogenesis etc.

Due to uneven bacterial invasion pathological process in the kidneys is not diffuse and may be even one-sided (unilateral).

Classification
There are the following forms of PEN:

* According to pathogenesis

1. primary;
2. secondary:
   1. obstructive, in anatomic anomalies of the urinary tract;
   2. in renal dysembryogenesis;
   3. in dysmetabolic nephropathies;

* According to the course

1. acute;
2. chronic:
   1. manifest recurrent form;
   2. latent form.

* According to the period

1. exacerbation (active);
2. development of reverse (partial remission).

* According to the function

1. without functional renal disorders;
2. with functional renal disorders;
3. chronic renal failure.

Chronic PEN is diagnosed when clinical and laboratory signs of PEN are observed for more than 6 mo.

Clinical picture. Clinical picture of acute PEN in typical case is characterized by:

1. pain syndrome (abdominal or lumbar pains);
2. dysuric disorders (imperative inclinations, pollakiuria, painor sensation of itch, burning during micturition, nocturia, enuresis);
3. symptoms and signs of intoxication (elevation of temperature with chill, headache, flabbiness, weakness, bad appetite, pallor with mild icteric tint).

The pain is markedly intensified in change of body position, jumps, inclines and is relaxed in warming of the lumbar region.

Edema is absent, as a rule, blood pressure (BP) is normal, diuresis is moderately increased. The urine is turbid, with an unpleasant smell.

Palpation of the ureter projection at the side of the lesion, in the renal region, in the angle between the
vertebral column and the last rib, is painful, as well as thrashing of lumbar region.

In urine there are:

1. leucocyturia - from moderate to significant up to pyuria; leucocyturia with more than 5-7 leukocytes in vision field is demonstrative, neutrophils are prevalent. In the absence of demonstrative leucocyturia it is necessary to carry out the tests of Amburgeau, Addis-Kakowsky, Nechiporenko;
2. bacteriuria - a colony count of over 100 000/ml can be taken as indicating significant bacteriuria. Evaluation of bacteriuria is made by taking into account of the type of a microorganism, its pathogenicity, the form and period of the disease, degree of activity of the process and patient’s age.
3. proteinuria - is not typical for pyelonephritis, usually is mild (1 g/l);
4. hematuria is not typical for pyelonephritis, but it sometimes occurs in secondary pyelonephritis;
5. restriction of tubular functions as to osmotic concentration (specific gravity is below 1020 while diuresis is less than 1000ml/d). The renal signs of the disease are the most important ones in diagnosing of pyelonephritis, the extrarenal signs in some children may be absent, in others they may be latent.

Data of excretory urography:

a) in acute pyelonephritis:
   - the kidney is enlarged by more than 1cm on the account of its parenchyma;
   - hypotonia of the ureters;

b) in chronic pyelonephritis:
   - asymmetry of the kidneys;
   - decrease of renal parenchyma as compared to contralateral;
   • significant variations of its thickness in the same kidney in different places;
   • deformation of calyco-pelvic system;

- irregular excretion of contrast substance up to adynamia of calico-pelvic system.

c) in chronic secondary pyelonephritis:
   - obstruction of the urinary tract;
   • congenital malformations;
   • reflexus;
   • renal dysplasia.

Common symptoms prevail in clinical picture of acute PEN in infants: flabbiness or anxiety, anorexia, hyperthermia, vomiting, constipation or dyspepsia, loss of weight, sometimes jaundice, convulsions, meningeal signs. Dysuric manifestations may be mild. Marked susceptibility to generalization of infection, rapid development of disorders of water-salt, protein and other kinds of metabolism, disorder not only of renal function, but also liver function with further appearance of severe intoxication and dehydration, collapse may be seen. The clinical picture resembles sepsis.

At the same time in infants with chronic PEN only such general symptoms as lack of appetite, insufficient increase of body weight and height, retardation of psychomotor development, subfebrile temperature may be revealed.

In older children the signs of intoxication prevail as well: apathy, flabbiness, headaches, bad appetite, disorders of nutrition, subfebrile temperature, abdominal pains of uncertain localization, rarely pains in lumbar region with minimal dysuric disorders or even without them. PEN may have latent course with minimal changes in the urine. There are chronic foci of infection in the great majority of patients.

Complications

Apostematous nephritis (lots of abscesses in kidneys). This is acute septic disease with high, more often of hectic type, temperature, marked intoxication and poor general condition (nausea, vomiting, convulsions, and dehydration).

Carbuncle manifests with squeezed calyces and pelvis or with amputation of one or few calyces on excretory urogram (as if it were tumor).

Paranecephritis. Lumbar pain is the main symptom; leucocytes appear in the urine later. High temperature may occur. Goldflame-Pasternatsky sign is positive. Sometimes the child lays in forced position with his leg bended in hip joint without limitation of mobility in it. This position occurs because of lumbar muscle contracture, which is stipulated by the inflammatory process. Fluoroscopy demonstrates limitation of lung margin's mobility and absence of renal displacement during respiration is seen. Swelling in the lumbar region appears more lately.

These complications of acute PEN in children are seen more rarely than in grown-up persons.
Nephrocalcinosis, nephrogenic hypertension, chronic renal failure due to arteriosclerotic kidney are complications of chronic PEN.

Diagnosis and differential diagnosis. In acute course or in exacerbation of chronic process there are no difficulties in diagnosis. It is necessary to carry out the following complex of investigations:

Urine analysis once per 7-10 days. If there are no clear findings for diagnosis, it is necessary to carry out Nechiporenko (Amburgeau, Kakovskiy-Addis) test. Revealing of the so-called "active leukocytes" in the urine sediment has some auxiliary significance.

Urine inoculation (not less than 3 times) with definition of microbe sensitivity to antibiotics. It is necessary to wash external genital organs with sterile tampons moistened in furacillin (including boys without circumcision of prepuce) and than with sterile water because they may be contaminated with microflora. It is important to wash girls from the front to back.

Determination of bacteriuria degree. It is considered significant if there are 100 000 of microbes in 1 ml of urine.

Determination of renal functional condition with 1) Zimnitsky's test once per 7-10 days; 2) Reberg's test; 3) determination of secretory renal function and renal blood flow. Besides it is desirable (in specialized hospitals it is obligatory) to determine the indices, which characterize the function of distal nephrons (ammonia, filtrated acidity of urine), proximal tubules (α₂-microglobulin in urine, proteinuria, calciuria, phosphaturia), Henle's loop (osmotic concentration of the urine).

Biochemical analyses of blood. Total protein, cholesterol, residual nitrogen are normal for a long time in PEN. Revealing of dysproteinemia (with elevated levels of α₂- and γ-globulins), rise of cialic acids, mucoproteins, positive C-reactive protein reaction are of diagnostic value.

Ultrasoundography of kidneys for establishing diagnosis of VUR.

X-ray and other investigations of the urinary tract 1 month after the acute period. Descending urography should be carried out in every patient with PEN (especially in infants). It is possible to reveal deformation or distortion, spasm of calyces or other parts of the urinary tract, disorder of excretory function of one or both kidneys, sometimes reflux. Radioisotope renography is useful in all patients with PEN as it gives possibility to evaluate excretory and secretory renal functions, asymmetry of their lesion.

Cystography and cystoscopy are obligatory for all children with dysuric disorders, enuresis.

Drawing up the genealogy with indication of all persons with renal pathology.

It is necessary to differentiate PEN from renal tuberculosis (contact with patient with tuberculosis is important). Hematuria and mycobacteria tuberculosis are revealed in the urine.

Differential diagnosis with glomerulonephritis is the most important.

Differential diagnostic signs of acute diffuse glomerulonephritis and acute pyelonephritis

<table>
<thead>
<tr>
<th>Signs</th>
<th>Acute glomerulonephritis</th>
<th>Acute pyelonephritis</th>
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<tbody>
<tr>
<td>Onset of disease</td>
<td>2-3 weeks after angina, scarlet fever, ARI</td>
<td>On the ground of acute bacterial and viral infections</td>
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<tr>
<td>Dysuric disorders</td>
<td>Not typical</td>
<td>Typical</td>
</tr>
<tr>
<td>Lumbar pains</td>
<td>Present in 25-30% of patients</td>
<td>Present in the majority of school age children</td>
</tr>
<tr>
<td>Temperature</td>
<td>As a rule, normal or subfebrile</td>
<td>As a rule, febrile or subfebrile</td>
</tr>
<tr>
<td>Urinary syndrome</td>
<td>Hematuria and cylindruria (sometimes leucocyturia in first 2-3 days), oliguria. Specific gravity is normal or elevated.</td>
<td>Leucocyturia, normal or elevated diuresis, monotonous, decreased specific gravity of the urine in different portions</td>
</tr>
<tr>
<td>Urine inoculation</td>
<td>Always sterile</td>
<td>Positive in 85% of cases</td>
</tr>
<tr>
<td>Residual nitrogen, urea</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Edemas</td>
<td>Typical</td>
<td>Absent</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present in most patients</td>
<td>Is not typical</td>
</tr>
<tr>
<td>Main indices of renal function:</td>
<td></td>
<td></td>
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<tr>
<td>Filtration</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Reabsorption</td>
<td>Normal</td>
<td>More often normal, but may be decreased</td>
</tr>
<tr>
<td>Secretion</td>
<td>Normal</td>
<td>More often decreased</td>
</tr>
<tr>
<td>Morphologic</td>
<td>Glomerular capillaries lesions are</td>
<td></td>
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It is established at present that PEN is a typical complication of hereditary tubulopathies, therefore it is useful to exclude these diseases by carrying out the following tests: daily excretion with urine of aminoacids (norm 0,001-0,005 g/kg), calcium (0,004-0.008 g/kg, but less than 300 mg/d), phosphates (0,01-0,04 g/kg, but less than 1 g/day), oxalates (0,001 g/kg, but less than 40 mg/day), citrates (0,006-0,012 g/kg), uric acid (<0,001 g/ml of urine, not more than 2 g/day), titratable acids (1-2 mmol/kg), ammonia (1-3 mmol/kg), urea (0,3 g/1g of protein in diet).

It is necessary to differentiate PEN from vulvitis, vulvovaginitis. If changes in urine do not disappear after the treatment of these diseases it is necessary to investigate the girl in suspicion to PEN.

It was proposed to differentiate PEN from infection of urinary tract with the help of urine bacterioscopy with labeled antisera to immunoglobulins G and A. If microbes are covered with immunoglobulins, the diagnosis of PEN is established.

Treatment. It is necessary to hospitalize the child in acute period. Bed rest in absence of renal insufficiency is indicated during the fever period and 3-4 days more.

If intoxication is present, the treatment is begun with forced diuresis. Daily quantity of liquid 1,5 times exceeds the age requirements. The patients receive supplementary liquid with water-melon, cranberries or red bilberries water, juices etc. Fresh vegetables and fruits, especially melons, vegetable marrow are of use. In acute period it is expedient to give milk-vegetable diet with moderate limitation of protein (1,5-2 g/kg) and salt (to 2-3 g). Diet limitations depend on salts in the urine sediment, its acidity.

In painful syndrome antispastic therapy is prescribed (no-spa, baralgin, papaverin).

If reflux exists, forced micturitions are useful (every 1,5-2 hours in squatting position).

Antibacterial drugs are necessary with preliminary urine inoculation and determination of microbe sensitivity. In presence of intoxication the treatment is begun with antibiotics - ampicillin, cefalosporins, and carbenicillin injected i.m. 3-4 times/day. Aminoglycosides are antibiotics of reserve. They are prescribed only if antibiotics mentioned above are not effective. Taking into account their potential nephrotoxicity it is necessary to administer them twice a day in middle therapeutic doses and not longer than for 7 days. Oliguria, renal insufficiency are contraindications for their administration. Antibiotics are used until intoxication and temperature disappear. After the antibiotics the course of lactobacterin is necessary.

Nitrofurans (5-8 mg/kg 4 times/day), nalidixic acid (negram, nevirgramon 50-60 mg/kg 4 times/day), 5-NOK, nitroxolin (8-10 mg/kg 4 times/day), biseptol (2 mg/kg of trimetoprim twice a day), sulphonamides (0,1 g/kg 4 times/ day) are used after a course of antibiotics.

After 2-4 courses of antibiotics alternative courses of uroseptics are prescribed for 3-6 months in acute PEN and 6-9 months in chronic PEN (10 days/month). If there are no signs of intoxication and high temperature, it is possible to begin the treatment with uroseptics without preliminary antibiotic therapy.

Phytotherapy is usually used. The types species are prescribed: diuretic, litholytic, antiseptic, antiinflammatory, consolidating vascular wall.

Physiotherapy is indicated as well. UHF-therapy or ultrasound therapy (5-8 treatments) are carried out in the acute period, later SHF-therapy (6-8 treatments) and then electrophoresis with 1% solution of furadonin and ampicillin (10 treatments).

It is necessary to reveal and treat in proper time the foci of chronic infection and sensibilization (dental caries, chronic tonsillitis, cholecystitis, helminthiasis, especially enterobiosis).

Treatment of VUR may be surgical or conservative. Ultrasound control of VUR is necessary every 6 months. Surgical correction of obstructive anatomical disorders is of great use, but antireflux operations in functional obstructions give the same effect as conservative therapy according to international group of experts.

Prognosis depends on the character of disease (primary or secondary), intensity of treatment, presence of accompanying diseases. If in secondary PEN it is impossible to liquidate the cause of urostasis, long term prophylaxis may be necessary to keep the urine sterile. At the same time, especially in infants, complete recovery is possible. Primary PEN is curable in 40-60% of cases, primary chronic PEN - in 25-35% of cases. But prognosis as to complete recovery is necessary to put very carefully after 5 years of observation and determination of renal function.