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BALKAN ENDEMIC NEPHROPATHY ORIGIN AND WAYS TO PREVENT THE CONNECTION

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Annotation: Balkan endemic nephropathy is a non-inflammatory tubulointerstitial lesion of the renal parenchyma in people living in endemic regions of the Balkans. It is manifested by asthenic syndrome, lower back pain, pallor and copper tint of the skin, xanthochromia, macrohematuria, polyuria, polydipsia. It is diagnosed by general and biochemical tests of blood, urine, ultrasound, MRI, CT, MSCT of the kidneys, general and excretory urography, nephroscintigraphy, histological examination of the biopsy. Patients are recommended for symptomatic anti-anemic, anti-ischemic, detoxification, renal replacement therapy, and kidney transplantation.

Key words: Balkan endemic nephropathy, kidneys, blood.

Balkan endemic nephropathy (BEN) was first described as Yugoslav nephritis in 1942. In 1956, there were reports of the detection of renal pathology with a similar clinical picture in residents of Bulgarian and Romanian villages. The BEN was recognized as an independent nosological unit by WHO experts in 1964. Most cases of non-inflammatory tubulointerstitial nephritis have been reported in rural areas of the Balkan countries (Bulgaria, Bosnia and Herzegovina, Romania, Serbia, Slovenia, Croatia) located on the tributaries of the Danube. The incidence in the foci reaches 30-33%. All endemic territories are located on plains surrounded by hills or in rivers, alternating with non-endemic regions. The majority of patients are 30-60-year-old rural residents. Before the age of 40-45, women suffer twice as often as men, but later this difference is leveled off. In urban residents, children and adolescents, the disease is usually not detected. Emigrants from the Balkan countries rarely get sick when they leave early. Immigrants may develop EBD after 15-20 years of living in the hearth.

Reasons

The etiology of the disease is not definitively established. Specialists in the field of urology and nephrology develop several theories of the origin of pathology, each of which is partially confirmed by statistical data and observation results. More extensive research is needed to definitively determine the causes of kidney damage in the Balkan region. Presumably, the etiological factors of endemic nephropathy can be:

- Infectious agents. According to the authors of the viral and prion theories of Balkan tubulointerstitial nephropathy, a chronic progressive course with a long asymptomatic period corresponds to signs of a slow infection. Indirect confirmation of the infectious genesis of the disease is the isolation of cytopathogenic agents from the biological substrates of patients and the possibility of infection of laboratory animals (guinea pigs, rats). The causative agent of BEN has not yet been identified, but the role of bacteria in the development of endemic nephropathy has already been completely excluded.
- Nephrotoxic mycotoxins. The theory that endemic Balkan nephropathy is a chronic ochratoxicosis is quite convincing. The main nephrotoxin is ochratoxin A, which is produced by some mold fungi and enters the human body with flour products made from contaminated grain. The main arguments in favor of the mycotoxic origin of the disease are the detection of an increased concentration of ochratoxin in the blood of residents of endemic areas and the similarity of pathomorphological changes with nephrological pathology in animals suffering from ochratoxicosis.

- Aristolochic acid. The theory of American scientists connects the development of Balkan nephropathy with the use of products contaminated with seeds of clematis kirkazon. This weed, which massively affects wheat fields of endemic territories, contains aristolochic acid, which has carcinogenic and nephrotoxic properties. In support of the theory, we used data on the development of "herbal Chinese nephropathy" in Belgian patients who took herbal preparations with kirkazone. The theory does not explain the lack of endemia in other regions where this plant is widespread.
- Pliocene lignites. Pliocene lignite deposits, the youngest brown coal variety in the Balkans, have been identified in most endemic areas. They contain aromatic amines that provoke the occurrence of uroepithelial cancer. Since such lignites have a loose structure, they are easily eroded by water and get into drinking wells of farms and rural settlements. The frequent development of squamous cell carcinoma of the ureter and pelvis in the Balkan regions with a high incidence of nephropathy indirectly confirms the common etiology of these diseases, but lignites are not detected in all endemic areas.
- Genetic factor. Since the endemic variant of nephropathy is often familial, some researchers have suggested the role of hereditary predisposition. In their opinion, the inherited mutation increases the sensitivity of the renal mesenchyme to the action of nephrotoxic modifying factors. It is possible that BEN is the result of dysembryogenetic disorders that lead to a decrease in the number of nephrons and a decrease in the functional reserve of the kidneys. The argument in favor of the genetic theory was the identification of changes in chromosome 3 in patients.

The role of environmental factors in the occurrence of endemic renal pathology is studied separately. In samples of soil, drinking water, and local food products, elevated concentrations of certain ions that have a nephrotoxic effect (vanadium, cadmium, manganese, copper, lead, chromium, etc.) are detected, some of which are found in large quantities in the biological tissues of deceased patients. The mechanism of development of nephropathy in case of mineral imbalance and their dangerous combinations have not yet been established. In addition, some urologist practitioners consider BEN as a variant of primary amyloidosis.

Pathogenesis

Although the mechanism of development of Balkan endemic tubulointerstitial nephropathy is still being clarified, scientists have managed to create a fairly complete picture of pathomorphological changes occurring in the kidneys. The trigger for the disorder is most likely the expression of a mutated gene or modification of DNA under the influence of a long-term effect of a possible provoking factor (ochratoxin A, aristolochic acid, virus, prion, aromatic amines, etc.). Autoimmune mechanisms can play a significant role in the formation of sclerotic processes.

The nephrons are usually the first to be affected: their basement membrane thickens, the glomerular mesangium expands. At the same time, there are hydropic dystrophic changes in the epithelium of the proximal tubules, which are subsequently aggravated by thickening, hyalinization, and stratification of the basement membrane. Active growth of interstitial connective tissue leads to the development of extracellular and perivascular sclerosis, which increases due to ischemia of the renal parenchyma against the background of thickening of the vessel walls, fibrosis of their intima and asymmetric narrowing of the lumen. The processes of fibrosis, sclerosis, stroma hyalinization, and atrophy of most of the proximal tubules and part of the glomeruli end in severe nephrosclerosis with a 2.5-4-fold decrease in kidney size up to 40-70 g.

Symptoms

Symptoms increase slowly, and at the initial stages they are non-specific. Usually, patients with Balkan nephropathy report weakness, rapid fatigue, loss of appetite, and minor pain in the lumbar region. Subsequently, the discomfort increases, periods of heaviness and dull pain in the lower

back are replaced by pain attacks. The skin becomes pale, sometimes with a copper tinge, on the palms and soles gradually turns yellow. As the nephropathy progresses, there is an intolerance to physical exertion, thirst, increased diuresis, dryness and insufficient turgor of the skin. Possible reddening of the urine due to the presence of red blood cells (macrohematuria). Edema is extremely rare. 20% of patients develop arterial hypertension.

Complications

Due to an early violation of erythropoietin synthesis, endemic nephropathy is still complicated at preclinical stages by normo - or hypochromic anemia, which leads to hypoxia of the brain, myocardium, and other organs and tissues. Residents of the Balkan region who suffer from kidney damage are 100 times more likely than those living in other territories to develop highly differentiated transitional cell carcinoma of the pelvis and ureters. This malignant neoplasm is detected in almost 40% of patients with BEN, and in 10% of patients the tumor process is bilateral. Pyelonephritis may occur when an infection is attached. In some cases, nephrolithiasis develops. The outcome of Balkan nephropathy is severe renal failure, leading to death from uremia with toxic multiple organ disorders.

Diagnostics

When making a diagnosis, the duration of residence in an endemic area, the dynamics of the increase in the clinical picture, and the data of laboratory and instrumental examination are taken into account. Diagnostic search is aimed at both verifying the disease and evaluating the functional viability of the tubular apparatus. Diagnosis of Balkan endemic nephropathy at the latent stage of the disease is usually difficult. In such patients, the significance of the geographical criterion significantly increases. The most informative research methods are:

- General urinalysis. It is characterized by a decrease in the specific gravity of urine below 1003, tubular proteinuria up to 1 g / day with the release of mainly low-molecular-weight β2-microglobulin, and at late stages — α1 -, α2-, β -, and γ-globulins, microhematuria. Glucose is often detected in the collected material.
- General blood test. An early diagnostic sign of BEN is anemia. The total level of red blood cells and hemoglobin decreases in patients with hypochromic hematopoiesis, the color index (CP) decreases. The content of leukocytes, the ratio of their types, ESR are usually not changed.
- Biochemical blood test. Insufficiency of the filtering function of glomeruli is detected at a late stage of nephropathy. The serum concentration of creatinine, uric acid, urea nitrogen, and macronutrients increases. Violation of renal filtration is confirmed by Rehberg's breakdown.
- Nephrological complex. Already at the pre-azotemic stage of BEN, the level of excretion of amino acids in the urine increases, and the release of ammonium and uric acid is disrupted. With the development of renal failure, the content of creatinine, urea, potassium, sodium, calcium, and phosphorus in the urine changes.
- Ultrasound of the kidneys. Echographic examination is more significant at the end stages of endemic nephropathy: the kidneys are symmetrically reduced in size, have a uniform structure, and do not contain calcifications. If necessary, ultrasound can be supplemented with an overview radiography, CT, MSCT, MRI of the kidneys.
- Histology of the renal biopsy. In the obtained material, signs of dystrophy and atrophy of the proximal tubules, edema of the interstitial tissue and endothelium of the stroma capillaries are determined, and individual macrophages are detected. At late stages, the morphological picture of tubulointerstitial sclerosis prevails.

To assess the filtration capacity of the kidneys, excretory urography and nephroscintigraphy can be performed. Endemic Balkan nephropathy is differentiated with chronic glomerulonephritis, pyelonephritis, analgesic drug nephropathy, cystinosis, intoxication nephropathy due to poisoning

with mercury, lead salts, and cadmium. According to the indications, the urologist or nephrologist involves an oncologist, toxicologist, or therapist to examine the patient.

Treatment of Balkan endemic nephropathy

Etiotropic therapy of the disease is not offered. Medical tactics are aimed at correcting symptoms, nephroprotection, and reducing the progression of BEN. To reduce the burden on the kidneys, it is recommended to refrain from heavy physical work, sufficient rest, and limit the consumption of salt, protein products, and water (taking into account the stage of Balkan nephropathy). Depending on the severity of clinical manifestations and the presence of complications, symptomatic therapy is performed, including:

- Antianemic agents. To stimulate hematopoiesis, iron preparations, folic acid, erythropoietins, and anabolic steroids can be used. Patients with severe anemia are sometimes transfused with red blood cells.
- Anticoagulants and antiplatelet agents. Improving the rheological properties of blood and renal blood flow can reduce ischemia and somewhat slow down fibrosis. In the end stages, medications of this group are not used due to increased bleeding.
- Detoxification. At the initial stage, enterosorbents and anti-azotemic phytopreparations are used. If renal failure increases, patients are transferred to replacement therapy (hemodialysis, peritoneal dialysis, hemofiltration, etc.).
- Kidney transplant. Donor kidney transplantation is a radical method of treating end-stage Balkan nephropathy. According to the results of observations, there were no cases of relapse of the disease in the transplanted kidney.

Prognosis and prevention

Pathological processes in the kidneys that occur in endemic nephropathy are irreversible and, in the absence of medical care, lead to death within 5-10 years from the onset of clinical symptoms of the disease. About half of patients die in the first 2 years after diagnosis of EB. Due to the unclear etiopathogenesis, prevention is difficult. As possible measures to prevent the development of uropathology, it is proposed to move residents of endemic foci to other territories as early as possible, and to exclude closely related marriages of family members who have been diagnosed with Balkan nephropathy. A possible positive role can be played by improving the environmental situation: high-quality water filtration, control of clematis-like kirkazon, fungal damage to grain crops, and control of food contamination with ochratoxin A. Secondary prevention is aimed at screening urological control of at-risk populations.

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