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BALKAN ENDEMIC NEPHROPATHY IN BULGARIA

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Summary. *Balkan endemic nephropathy (BEN) was described in Bulgaria, in the district of Vratsa in 1956, and for more than 40 years this disease has been the subject of extensive studies. In this review, the author describes: geographic and physico-clinical characteristics of the endemic region, epidemiology of BEN, etiology, pathomorphology and morphogenesis, clinical picture, and one of the most interesting finding in BEN - the unusually frequent combination of parenchymal renal injury and uroepithelial tumors of the urinary tract. Most frequent are tumors of renal pelvis, followed by tumors of ureter and urinary bladder. All these facts make BEN more mysterious and interesting, and the efforts and means for clarifying its nature and etiology are worthwhile.*

Key words: *Balkan endemic nephropathy, epidemiology, etiology, morphology, clinical features, urinary tract tumors*

The first studies on endemic nephropathy in Bulgaria are dated from 1949. In the same year, L. Ivanov carried out clinical and laboratory examinations of the population from the villages most affected by the disease in the district of Vratsa and published his results in 1956 (1). The first description of endemic nephropathy as an independent nosological unit was made by G. Majdrakov in 1954 (2,3,4,5). For more than 40 years this disease has been a subject of profound studies by physicians, epidemiologists, pathomorphologists, microbiologists, virologists, mycologists, geneticists, physicists, chemists, geologists, hydrologists, radiologists, zoologists, veterinary surgeons, public health specialists, etc. Detailed information is accumulated about different aspects of the disease. The first monograph – "The endemic nephritis in Bulgaria" was issued in 1960, followed by many symposiums, dissertations, scientific publications in the three countries affected by the disease. This prompted the publication of a new monograph – "Balkan endemic nephropathy" edited by Ts. Dimitrov in 1984.

Geographic and physico-chemical characteristics of the endemic region

Endemic nephropathy is established in well-defined regions of Bulgaria, Romania and the countries of former Yugoslavia. In Bulgaria this region is situated approximately between the Ogosta and Malki Iskar rivers near the north mountain sides of the Vratza's Balkan and Stara Planina, with 100 km in length and 30 km in width (5). The endemic settlements are situated on a drainable terrain without conditions for swampyshing. The region is situated almost completely on one synclinal (the Calashk's synclinal), created predominantly of Downcretaceous sandstone, limestone and marls, and uppercretaceous limestons. The water for the affected settlements passes through the same strata. Because of the hilly and karst character of the terrain the underground waters circulation is superficial and fast, that is why they are poorly mineralized and more abundant in organic substances.

The content of a number of elements of great biological significance for the organism which are known or supposed to influence the renal diseases has been estimated in the potable water. Kusitaseva, Grancharov, Micev (1960) estimated the content of lead, zinc, copper, cobalt, mercury, chrome, arsenic, barium, iron, manganese, fluorine and uranium in the potable water and that it is quite variable but within the borders of the utmost admissible concentrations (6).

Nikiforov (1960) received similar results for iron, titanium, aluminium, chromium, copper, lead, zinc, tin, cadmium, bismuth, molybdenum, nickel, cobalt, vanadium, tungsten and uranium in potable water from Bistretz village (7).

Bojadgiev et al. (1965) found high concentrations of phosphates in comparison with water from unendemic villages (9).

Bachev et al. (1966) found elevated levels of lead and cadmium. In certain periods of the year – usually summer-autumn, the concentrations of manganese, copper and cobalt are increased (10).

Angelieva and Mladenova (1979) have found increased concentrations of manganese and cadmium in comparison with the control water samples (11).

The content of a number of heavy metals is estimated in samples of soil and rock. The content of cadmium, cobalt, copper, lead and zinc in the weather crust of the endemic region reaches the admissible concen-

tration and slightly surpasses it in separate samples. It is accepted that the increased concentrations of some trace elements in the spring water is due not to the superficial Cretaceous strata but more to those, placed under them, with larger compact or scattered ore touches. The concentrations of manganase and cadmium in soils from the endemic region are insignificantly increased (11).

The analysis of the results received from the examination of the water and soil samples for their content of trace elements found that the concentrations of aluminium, manganase, cadmium, chrome, lead, copper and cobalt are most frequently increased. Their importance for the physico-chemical characteristics of the endemic region and in what degree this mineral content represents its specific characteristic is still not cleared but it could give some directions for future investigations.

Epidemiology

The endemic nephropathy is observed only among the village population. Because of the intensive urbanisation in the recent decades cases of endemic nephropathy are established in towns but these are emigrants from the endemic villages and their children. The endemic villages are grouped together but there are among them some where there are no cases of endemic nephropathy. The endemic settlements are affected by the disease in different degrees, because of that we classify them as hypoendemic, mesoendemic and hyperendemic. In the endemic villages the found morbidity of endemic nephropathy is – 770/00 and mortality – 1810/00; in the mesoendemic – morbidity – 4490/00 and mortality – 790/00 and in the hyperendemic – morbidity – 5938/00 and mortality – 4880/00. The exact number of patients has never been known. This is so because the patients in the early and latent stages always remain unknown. In the period 1961-1972 2182 patients are registered, as 865 (39.6%) died (5,12,13). In the recent twenty years the activity of searching for these patients by screening examination of the population of endemic villages is completely ceased which gives a reason to think that the morbidity of endemic nephropathy is decreased. We carried out a rescreening in the village of Gorno Peshtene 15 years after the first one, and we found new 74 patients of endemic nephropathy unknown up to that moment. This fact supports the attitude mentioned above (14).

The mortality of endemic nephropathy in the endemic villages is extremely high – it is over 50% of the total morbidity. Because of the familial nature of disease, for suffering families this disease creates biological problems of surviving (5,12,13).

Age and sex of the patients. There is no observed clinical evidence for the disease up to 20 years of age. The most affected age is between 40 and 60 years of age. The results of the clinical-laboratory, instrumental and nephrobiopsy examinations we carried out on clinically healthy subjects, originating from families with endemic nephropathy at 8 to 20 years of age revealed that the onset of the disease is in childhood, has a long latent course and its clinical manifestation is in the later age. The women are more frequently affected. The disease has pronounced familial nature and this is of great importance for its diagnosis (5,12,13,15).

Suffering of emigrants and immigrants. A great number of emigrants from endemic families in nonendemic settlements including towns, who developed endemic nephropathy, i.e. their parents' disease, were observed in our country. We also established cases of endemic nephropathy among the children of affected emigrants, born in the new, unendemic living place of their parents. There are no proved cases of endemic nephropathy among the immigrants into the endemic settlements (16,17).

Domestic and wild animals in the endemic region. Profound studies are carried out on domestic and wild animals in the endemic region searching for cases of endemic nephropathy. The authors of these studies found that the domestic and wild animals did not suffer from endemic nephropathy (18,19,20).

Etiology

Three basic hypotheses are created about the etiology of endemic nephropathy – infectious, toxic and genetic (1,2,15,56).

The infectious hypothesis suggests a relation of the endemic nephropathy to living agents – bacterial, fungial, viral. There is no evidence for the relation of the disease with any kind of bacterial strains.

M. Dimitrov (1960) isolated four toxic fungial strains from cereals from the endemic regions. The results of the experimental studies did not allow him to accept any casual relationship of these fungi with the endemic nephropathy (21).

Krogh (1979) demonstrated toxic concentrations of ohratoxine A in cereals, used for nutrition of the population in endemic regions. This gave him a reason to assume that the endemic nephropathy is a nutritional toxicosis. These data have to be seriously specified further (22).

Profound studies were carried out searching for viral agents. Schindarov et al. (1965) did not establish a relation between the disease and viral agents. Rusakiev and Dochev (1971) systematically inoculated monkeys with materials of patients who died of endemic nephropathy. None of the experimental animals revealed signs of endemic nephropathy for a number of years (23,24).

Andonov et al. (1978) isolated several viral agents from tumors of the urinary tracts of patients with endemic nephropathy. (25) The authors succeeded to reproduce by them tumors in experimental animals, accompained by myeloid leukosis, inflammative foci in the exaggerated spleen, in the mesenterium, and also in the kidneys with alterations of glomerules, destructive alteration in the tubular epithelium, hyaline cyringes and haemorrhages. A significant amount of viral particles were found by electron microscopy of the tissue of the experimental animals. However, the authors do not conclude that these viral particles are in causative relation

with the endemic nephropathy. Independently of that, the frequent combination of the endemic nephropathy with uroepithelial tumors gives a serious reason to search tenaciously for a relation of the disease with viral agents. It is necessary to clarify the possibilities of slow-virus infection, of viral-genetical mechanism, etc.

Hypothesis for intoxication with trace elements. A number of facts give a reason to assume that in the endemic nephropathy what is possible is a slow development of intoxication of organism with prevailing damage of the kidneys. The disease remains located in the endemic villages for decades. The disease is revealed clinically after 20-30 years of age. The morphological alterations of the kidneys of dead patients are very similar to these in the chronic heavy metal intoxication. The functional examinations reveal earlier and heavier damaging of the tubular function, as in heavy metal intoxication and in chronic interstitial nephritis of toxic origin. There are described morphological alterations of the liver resembling these in chronic intoxication. There is a reason to assume a toxic damage of the bone marrow. The parenchymal renal damages are very frequently combined with papillomes and papilar cancers of the urothelium. These data are a reason to look for the causes for the endemic nephropathy among different environmental components of the endemic regions (2,15).

The synthetic analysis of the results from the examination of the potable water, soils and most frequently used foods in the endemic settlements reveal some increase of the concentrations of some trace elements as lead, cadmium, manganese, copper, cobalt, uranium, aluminium, chrome, tungsten, silver and zinc. For most of them it is known that they have a nephrotoxic effect but their casual relationship with the disease is still not clarified (6,7,8,9,10,11).

Stefanov et al. (1960, 1964, 1967 ,1971) on the basis of experimental studies of potable water from the endemic region and controls expressed the opinion that it is possible the endemic nephropathy represents a slowly progressing uranium intoxication occurring in a common concentration of uranium in the water but in the interaction with other elements, potentiating its action – lead, phosphorus, cadmium, cobalt, etc. (26,27,28).

Donev, Dragnev, Dincheva (1965) estimated hystoradiographically the content of polonium, torium and uranium in kidneys, liver, spleen, lung and bowels of deceased from endemic nephropathy. There were not found level, higher than the internationally accepted standard in any of the examined organs (29).

Makarov et al. (1971) examined viscera and bones of the deceased of endemic nephropathy and controls for cadmium, lead, zinc, aluminium, copper, tin, molibdenium, nickel, chrome, titanium, cobalt, bismuth, silver, barium, manganese and strontium. Considerably increased concentrations of aluminium, tin, nickel and chrome and single cases of lead, manganese, barium, bismuth and titanium are found in the examined organs, especially the kidneys (30).

At present, it is difficult to evaluate the significance of abnormalities found in the trace elements concentration in the organs of the deceased of endemic nephropathy. If some of them or all together are related with the etiology of the disease by entering the patients organism in greater amounts, it is logical they are to be in abnormally high concentrations in the environmental factors of the endemic regions. Such are found only for aluminium, chrome, lead and manganese. The rest of them – tin, nickel, barium and titanium are still not found in increased concentrations in the environment of the endemic settlement. Hence, the increased organ retention of the tin, nickel, barium, bismuth and titanium could not be the exogene mechanism only. This requests the consideration of endogene mechanisms – their exact type is still not known.

The established data for an abnormal content of some trace elements in the environment of endemic regions, as well as in the organs of the deceased of endemic nephropathy are important arguments, supporting the hypothesis of the chronic, cumulative metal intoxication. It is difficult to assess the role of different trace elements or their complex at the level of our recent knowledge. At any rate, the established facts are an important stage of studying the etiology of this disease and they reveal prospects for further scientific and research work towards the clarification of their role and significance for the etiology of the endemic nephropathy.

Genetic hypothesis. A number of facts give a reason to assume also genetic factors in the etiology and genesis of the endemic nephropathy. This disease has an expressed familial character. (31,32,33,34,35,37) The genealogical studies reveal autosome-dominant type of inheritance. We have observed emigrants of suffering families, settled at a half, 3 and 6 years of age in nonendemic regions, where after 57, 25 and 27 years respectively they died of endemic nephropathy, i.e. their parents disease. The son of the emigrated at a half year of age, who was born in the nonendemic place of residence of his father and lived permanently there, suffers from endemic nephropathy at the moment with the first degree of chronic renal failure (proved by biopsy) (16).

In 1959 it was decided to move the people of Karash village – one of the most affected by the disease. Its inhabitants settled predominantly in the villages near the City of Sofia (nonendemic region). Our 40-year lasting observations revealed that a great number of persons, originating from the suffering families, died of endemic nephropathy in their new places of residence. As a result of many years of citogenetic studies we established in 1984 a presence of a shorter long arm of the one haploide of the third couple of chromosomes with a strongly narrowed 3q25 band, accompanied by inadequately quick fusion of the 3q26.1 and 3q26.3 subbands and undifferentiation of 3q24 band in all examined patients with endemic nephropathy and in 50% of their still clinically healthy children. The nephrobiopsy of their kidneys, revealed characteristics for the early stages of the endemic nephropathy. These alterations in the third couple of chromosomes we accepted as a chromosomal marker which can give us the diagnosis of endemic nephropathy in every of its stages, including

the childhood. We consider it could be used for the antenatal diagnosis of the disease. All these data give us a serious reason to consider the endemic nephropathy as a genetically determined disease. The future molecular biological studies will probably illuminate better, and maybe sufficiently this aspect of the endemic nephropathy (35,36,37,56).

Pathomorphology and morphogenesis

The pathological and hystomorphological characteristics of the endemic nephropathy are described in our country on the autopsy material from 250 deceased and over 60 kidneys from nephrectomies because of tumors. The early morphological renal alterations are described on biopsy samples taken by open or punctional biopsy of 60 clinically healthy persons, originating from heavily hereditary burdened families with endemic nephropathy, at more than 8 years of age (32,33,38,40,41,42,43,44).

On the basis of clinical-morphological criteria in the course of disease there can be differentiated with some conventionality the following stages: initial, subclinical and clinically expressed – compensated and decompensated.

Morphological alteration in the initial stage

The alterations in that stage are described on samples of renal biopsies, taken from the relatives of patients and the deceased of endemic nephropathy at over 8 years of age (33,38,39,5). The pathological alterations are localized predominantly in the external zone of the renal cortex. The histological alterations in glomerules are characterized by an extension of mesangium due to increased secretion of mesangial matrix and slight proliferation of the mesangial cells. The corresponding part of the basal membrane of the capillary stitches is unequally thickened. Microaneurysmally distended capillary stitches are found in some glomerules. A small number of glomerules are with the picture of a glomerular collapse. In some of the samples there was found a presence of fetal glomerules. The alterations of electron microscopy picture are also of focal type. The pathological alterations of the tubules in comparison with the glomerules are more extended and expressed in a greater degree. The alterations of the proximal tubules are most severe. They are characterized by severe dystrophic and necrobiotic alterations with picnosis, cariorexis and a reduction up to entire vanishing of the DNA from the nuclei of the epithelial cells. The epithelium of the tubules of adjacent nephrons is high and expresses signs of increased functional activity. By electron microscopy there are found wrinkled and picnotic nuclei of the cells of the proximal tubules. The cytoplasm of these cells is with a vacuolic dystrophy. The smooth and the granulated endoplasmial reticulum are vesicularily transformed and fragmented. The mitochondrias are swollen, plumped, the number of crists is diminished, while some of them are lysed. There are observed mitochondrias, whose matrix is strongly lightened and in it are found matrix agregates in the shape of round, undistinctly outined amorphous osmiophylic formations with dimension of 0.1–0.5 nm in diameter, placed separately or in groups. In the cytoplasm of some of the tubular cells are found osmiophillic pilings, similar to these of the mitochondrias, which are not covered by membrane structures. The number of cytosomes is increased and they consists of single, plumpy, with high electrone density particles. The basal membrane of the damaged tubules is unequally thickened, frequently stratified. Vesical alterations are found only in the small arteries and arterioles – swelling of the vessels walls with PAS-positive protein substance, located under the internal elastic membrane, and segmental proliferation of smooth muscular cells, which sometimes cause deformation and narrowing of the vessel lumen.

The ultrastructural alterations in the glomerules and the proximal curved tubules described in the initial stage of the endemic nephropathy are similar to these, found in the clinically manifested forms of the disease. The glomerular damages are similar to these of the chronic lobular obliterating glomerulitis. The tubular lesions are located predominantly in the proximal tubules and like the tubular damages in the advanced stage of the disease they are distinguished for a greater incidence and severity. There is nothing specific in the glomerular and tubular damages, considered separately from each other. The glomerular damages of that type could be found in glomerulopathies of absolutely different nature. The pathological alterations in the proximal tubules represent also unspecific signs, which could be observed after different influences on the tubular epithelium. For the renal damages what is characteristic in the initial stage of endemic nephropathy is the combination of focal glomerular lesions with more expanded tubular damages – as it is in the clinically manifested forms of the disease. Relatively characteristic is the osmiophillic, amorphous agregate in the mitochondrias of a significant number of the proximal tubular epithelia, which are found quite often in the advanced phases of the disease.

Morphological alterations in the subclinical stage

The renal alterations in patients at subclinical stage of endemic nephropathy are observed in samples of nephrobiopsies. This material is obtained from individuals aged from 20 to 45 who were born and have lived in endemic regions, who have sick or dead relatives from the same disease and who themselves show discrete signs of the disease. At this stage glomerular, tubular, vascular and interstitial alterations, predominantly in the external zone of the renal cortex are established (32,33,40,41).

Glomerular alterations. Glomerular alterations are of focal-segmented inflammatory type with different intensity and some of glomerules show partial or total hyalinization. Most severe are the alterations in the juxta glomerular apparatus. In fact, glomerular alterations at this stage are of the same type as at the initial stage but are much more manifested.

Tubular alterations. Tubular alterations are also focal and their location corresponds to the damaged glomerules. The cells of the proximal tubules are mainly affected and they show the picture of granular-dropp dystrophy. The basal membranes in the regions are thickened. Gradually a tubular atrophy is developed. The alterations in the distal tubules concern their basal membranes which are thickened but to a considerably lower degree than are the basal membranes in the proximal tubules.

Interstitial alterations. The first interstitial alteration observed is the presence of homogeneous substance between the tubular basal membrane which resembles a serous exudate. Among the atrophic tubules a fibrous tissue abundant in argyrophilic fibers appears. It is definitely cell deficient tissue that replaces the destroyed tubules, i.e. there is an incipient noncellular interstitial sclerosis.

Vascular alterations. Segmental pathologic alterations in the small arteries, arterioles and venules are established. Their walls are irregularly thickened and their lumen is asymmetrically narrowed. In some of the small arteries besides the precipitation of protein substance under the intima, a segmental muscular cell proliferation is observed. There is a periglomerular and perivascular dilatation of the lymph vessels.

Immunomorphological assay of a biopsy material shows predominantly segmental coarse-grained precipitation of IgM and C3 fraction of the complement in the injuried glomerular segments, as well as precipitation IgM and mainly C3 in the arteriolar walls. When there is a more intensive C3-fraction precipitation, it can also be observed in the adjacent regions of Bowman's capsule or in the basal membrane of adjacent tubules.

Pathologic alterations of the renal structures at this stage are focal and still poorly manifested. The prevalent part of renal parenhyma is intact. That is why the clinical manifestations of the disease are slight and insignificant.

Morphological alterations at the advanced stages

The advanced stage of the disease is the most completely and detailed pathologically and histomorphologically investigated. The description of its morphological characteristics is obtained from a great number of dead patients (42,43).

In all deceased patients the kidneys are extremely diminished. Their weight reaches 40 g. Their surface is completely smooth. Histologically, two zones of the renal cortex are distinctly outlined: external zone next to the capsule with severe interstitial fibrosis, single intact glomerules, atrophy and disappearance of the tubules; and internal zone – including the rest of the cortex and the Bertini's column with much milder interstitial sclerosis, great number of intact glomerules and with predominantly atrophic and dystrophic alterations in the epithelium.

Glomerular alterations. In the external cortical zone the glomerules are homogenous, structurless, extremely diminished globules. In the internal zone a small part of the glomerules are intact or completely hyalinized. The greatest number of damaged glomerules are at different disease development stages. Pathological alterations are of the same type as in the preceeding stages but at a considerably more advanced phase of development.

Tubular alterations. Most severe are the alterations of contortial tubules in the external renal cortex. They are atrophic and the greatest number of them have no epithelial layer. Their basal membranes are wavy and thickened. Tubuli renalis collagens are moderately narrowed and with cuboid or plane epithelium.

Vascular alterations. All renal vessels have media and intima thickened. The internal elastic membrane is rough and thickened. There is a great amount of new elastic fibers near the adventitia which formed a perivascular net. The media thickness and a proliferation of connective tissue is observed as well. There are extremely dilated lymphatic vessels.

Interstitial alteration. Most severe are the interstitial alterations in the external cortical zone. Destroyed glomerules and tubules are replaced by diffuse connective tissue proliferation. Connective tissue is comparatively poor in cells and abundant in collagen and is either finely reticular or coarse fibrilar. In some regions a connective tissue stripes can be observed which starts from the external zone of the cortex, passes through the internal zone of the cortex and continues in the pyramids. The fibrous regions of the internal cortical zone show interstitial round cell infiltration.

The results of the morphological investigation show that the renal pathological process in endemic nephropathy has a very slow course. Its onset may be in infancy and have a very long latent period.

A distinguishing morphological feature of the disease is a frequent presence of concomitant urinary tract tumors. Most of them are uroepithelial papillary cancers at different degrees of malignity.

Few of them are planocellular cancers. The tumor location is a good basis for urinary drainage disturbance and for a possible superimposed acute or chronic pyelonephritis occurrence.

Clinical picture

Our long lasting studies (since 1962) of endemic nephropathy and mostly of its prenitrogenemia phase show that this phase has a very slow course and is much more continuous than the nitrogenemia phase. For that reason we consider that all preceeding clinical classifications do not cover completely enough and exactly the existing phases in the clinical course of the disease (5).

On the basis of results of complex clinical-laboratory, functional, instrumental and morphological studies to date we accept the following stages in the clinical course of endemic nephropathy:

1. Initial stage
2. Subclinical stage
3. Stage of compensation with manifested renal symptoms and serum creatinine not elevated.

4. Stage of decompensation with chronic renal failure at different extent.

Initial stage

Diagnosing of the endemic nephropathy at an initial stage is extremely difficult. The established slight clinical-laboratory abnormalities are non-specific and have no diagnostic value. Nevertheless, findings such as weak paint in the abdominal and lumbal region, low-grade intermitent proteinuria, transient changes in blood casts in urinary sediments, mild and even transient normochromic or hypochromic anaemia, typical dysaminoacidemia (hyperprolinemia and hyperalaninemia) and possible malformation of the urinary system of children and adolescents from endemic regions especially if they have a family history for the disease and have no nephrotic syndrom and arterial hypertension should suggest endemic nephropathy at an initial stage. Diagnosis can be confirmed only by renal biopsy and histomorphological and electro-microscopical examination, respectively. Nowadays we are considerably helped in diagnosing an early stage of the disease by using a chromosome marker 3q25 (33,35,36,37,38,39).

Subclinical stage

For many years patients with endemic nephropathy look for a doctor only when a clinical picture of advanced renal failure is present, and frequently when uremia occurs. For that reason there was a wrong concept for a brief course of the disease. This was a consequence of having no acquaintance with the early signs of the disease.

It was natural to assume that there was a long preclinical stage, unknown for us till then. This focuses our attention on investigation of early subclinical disease manifestations. We have investigated and studied clinical-laboratory, functional, instrumental and morphological features of subclinical stages of endemic nephropathy in apparently normal individuals over 20, who had sick relatives and lived in endemic regions. We have followed up the results of these investigations for more than 30 years (32,33,44,45,46,47,48,49,50,51,52,53).

The initial stage of the disease is followed by the subclinical stage. Renal parenchymal morphological alterations are more advanced and extensive than in the preceeding stage, so they may bring about already recognizable manifestations of the disease. The patients complain of intermittent dull, sometimes sharp pains in the ural region with no urination disturbances. Haematuria, due to papillomas in urinary tract occurs in 3 per cent of the cases. Hence, endemic nephropathy may be manifested as early as this stage as uroepithelial tumor.

The most frequent symptoms are a copper-like to pale colour of the face (33.6%), palmar and plantar xanthochromia (12%), positive succusio renalis (10%). There is no arterial hypertension and oedemas.

Laboratory assays may show high erythrocyte sedimentation rate, mild normochromic anaemia, hyperprolinemia and hyperalaninemia, intermittent low grade proteiuria, and in some cases – erythrocyturia. Renal concentration and dilution is not disturbed. We have no case with bacteriuria. Radioisotope investigation shows a mild elongation of secretory-excretory phase on the isotope nephrogram, and scintigraphy shows a slight diffuse space out of the radioactive impulses. Renovasography frequently shows the presence of a shorter trunk of renal arteries (below 4 cm), hypoplastic kidneys, fetal lobulated kidneys, accessory kidneys, segmental hypoplasia (54).

It is necessary to emphasize that at this stage only the renal biopsy or detection of the chromosome marker can give a firm diagnosis. If application of the methods is impossible, only continuous follow up of these patients may confirm the diagnosis.

Stage of compensation with manifested renal symptoms

Nephron damage is considerably more severe at this sage than at the preceeding one. This accounts for more complete clinical, laboratory, and functional manifestations, typical of the disease. However, renal function is still compensated mostly for non-protein and nitrogen-containing substances (15,5).

Medical history enlarges gradually and complaints become more constant. Lassitude and rapid fatigue after physical exercise and slower recovery occur. Appetite and weight are reduced. Some patients complain of headache and vertigo. Liquid consumption rises and polyuria occurs. A great deal of patients complain of dull pains in renal region, which in certain moments become tight or sharp. In some patients haematuria occurs and sometimes it is accompanied by a typical renal colic. Except for these cases, the patients at this stage usually have no urination disturbances.

Physical examination shows much more expressed copperlike to pale complexion, palish mucous membranes, dry skin with reduced turgor, more frequent and more intensive palmar and plantar xanthochromia, lack of oedemas and arterial hypertension and no findings when cardiovascular, respiratory and digestive systems are examined.

Laboratory tests establish a constant low grade tubular pattern proteinuria with poor urinary sediments, except when haematuria, reduced specific gravity to hypostenuria occurs. There is already constant hypo- or normochromic anaemia with high erythrocyte sedimentation rate.

Uric acid, sodium and chloride excretion is reduced while the excretion of urea, creatinine and potassium is not disturbed. There is a slight reduction of glomerular filtration and a greater reduction of the effective renal plasma flow.

The assay of protein metabolism shows normal total blood protein and raised values of beta and gamma globulines and beta 2-microglobulins. At this stage hyperprolinemia and hyperalaninemia with hyperprolinuria and hyperalaninuria are present as well. Typically, there are vitamin A metabolism disturbances, which result in

hypervitaminaemia "A" and hypobetacarotinaemia.

Radioisotope and X-ray examinations establish a secretory-excretory function disturbance, diffuse radionuclide incorporation disturbance and reduced renal size. We have established the presence of chromosome marker 3q25 in all examined patients. Diagnosis at this stage is not difficalt.

Stage of decompensation

The stage of decompensation includes a clinical manifestation of the stage of compensation, i.e. the manifestation of the very endemic nephropathy and of the incipient and developing chronic renal failure. At this stage the symptoms of the respective chronic renal failure degree are prevailing. The disease results in terminal renal failure with consequent haemodialysis or death. There are some cases with renal transplantation and these patients are among the patients who respond to transplantation treatment. Having in mind the facts already discussed, I find no need for further detailed clinical picture review of the disease at this stage (5,15).

I would like to quote the position of A. Puhlev, who puts the clinical features of endemic nephropathy in two groups: specific and characteristic features. Specific features are: endemic type, familial type, the late onset, early anaemia, specific blood and urine aminoacid constellation and unusually frequent combination of the disease with uroepithelial tumors. Characteristic features are: the lack of acute onset, peculiar colour of the face, palmar and plantar xanthodermia, the absence of nephrotic syndrom and arterial hypertension, peculiar changes in carotin and vitamin "A" metabolism and low grade proteinuria and poor urinic sediments.

Endemic nephropathy and urinary tract tumors

One of the most interesting findings in endemic nephropathy in Bulgaria is the unusually frequent combination of parenchymal renal injury and uroepithelial tumors of the urinary tract. Such a combination and such frequency have not been described in other chronic renal diseases yet. Besides, the tumor formations show many characteristic features.

Petrinska (1960) found a combination of endemic nephropathy and papillar tumors of uroepithelium in 48.4% of post-mortem examined individuals with endemic nephropathy (42). Mihailov reported 40% (43). In 90 patients uroepithelial tumors were 41% (5). The part of pelvis renal tumors was 68.6%, ureter tumors – 32.6% and urinary bladder tumors – 13.3%. Multiple location (renal pelvis – ureter, renal pelvis-urinarybladder, ureter – urinary bladder, renal pelvis – ureter, urinary bladder and ureter, urinary bladder, stomach) was observed in 14% of the patients. During the hemodialysis we have detected uroepithelial tumors in patients with endemic nephropathy. Our observations of emigrants coming from the endemic to nonendemic regions show that in patients with endemic nephropathy which appears while living in nonendemic regions the rate of concomitant uroepithelial tumors is the same as in the endemic regions (5,57,58,59).

Most frequent are renal pelvic tumors, followed by ureter tumors and urinary bladder tumors. This rate is just the opposite to the statistic rate observed in the regions around the world which is as follows: most frequent are urinary bladder tumors, followed by ureter tumors and renal pelvic tumors. All these facts make Balkan endemic nephropathy more mysterious and interesting and the efforts and means for clarifying its nature and etiology are worthwhile.

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