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The value of electron microscopy in the diagnosis of renal disease

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ABSTRACT

In the literature of recent years there are few publications on the importance of research in electron-microscopic pathomorphological diagnosis of kidney disease. The most important, which is diagnosed only on the basis of these studies are: minimal change disease, assessment of mesangial cell proliferation as well as the differentiation of the types of membranoproliferative glomerulonephritis, fibrillary glomerulonephritis, lupus nephritis, thin basement membrane disease, Alport syndrome, hemolytic-uremic syndrome. This report presents the most characteristic features of the ultrastructure allowing for diagnosis of these diseases.

Keywords: renal biopsy; kidney; electron microscopy.

Percutaneous kidney biopsy was introduced in clinical practice in the early 1950s. The first biopsies were carried out by Alwall on 13 patients already in 1944, however, the death of one of his patients discouraged Alwall from using biopsy as he considered it too risky [1]. He published his experience with renal biopsy only in 1952, one year after the publication by Iversen and Brun, who are considered the pioneers in this area [2]. From then on, biopsy of the kidneys was applied more and more often. At the same time, the technique of electron microscopy was introduced.

In Poland, electron microscopic examination was first introduced in Poznań by professor Janusz Groniowski in 1961. Kidney biopsy was applied earlier in Gdańsk, but without ultrastructural analyses.

To be emphasized is the fact that it was in kidney biopsies, that electron microscopy was applied for the first time to solve problems of human pathology.

Thanks to that research, a series of morphological and functional connections were discovered, in particular concerning the mesangium, the glomerular basement membrane and the juxtaglomerular apparatus.

Electron microscopic analyses made it possible to explain the character and location of series of changes observed in optical microscopy and revealed changes not discerned in optical microscopy.

At present, for 10–13% of biopsies, electron-microscopic analyses improve the initial histopathological diagnosis, and in 30–40% of the cases they serve to broaden the information obtained by optical microscopy.

Without examinations of the ultrastructure, the classification of glomerular diseases would have been impossible.

The best examples of diseases the diagnosis of which is based exclusively on electron microscopy are: minimal change disease, assessment of mesangial cell proliferation as well as the differentiation of the types of membranoproliferative glomerulonephritis, fibrillary glomerulonephritis, lupus nephritis, thin basement membrane disease, Alport syndrome, hemolytic-uremic syndrome.

Minimal change disease

The diagnosis of this glomerulopathy is based on changes concerning the podocytes consisting in the enlargement and subsequent effacement of the foot processes as well as the growth of microvilli on the sur-

face of the podocytes. The latter is of essential significance, as it lasts longer than the foot process effacement and helps to establish the diagnosis when the biopsy is performed after the application of treatment. The process effacement then in general no longer concerns 70% of the capillary loops, which is required for the diagnosis of this glomerulopathy [3, 4].

Assessment of mesangial cell proliferation

Sometimes very difficult to assess by histologic examination is mesangial cell proliferation. Endothelial cells and/or podocytes can, due to their location in the immediate proximity of the mesangial areas, erroneously be included in the mesangial areas and lead to the diagnosis of mesangial cell proliferation. This occurs in particular when the changes are not very pronounced and can even result in an erroneous diagnosis of mesangial proliferative glomerulonephritis. Obviously, immunofluorescence is equally of basic significance for the diagnosis of this glomerulopathy, but the material for this examination cannot always be obtained or the result of the reaction is uncertain. Then, a reliable diagnosis depends on the correct assessment of the mesangial hypercellularity (from 4 cells up) and the discovery of deposits in the mesangium [5–9].

Membranoproliferative glomerulonephritis

Electron microscopy is also essential for the diagnosis of the relevant type of membranoproliferative glomerulonephritis. All 3 types present the same optical microscopy image, i.e. a splitting of the glomerular structure, an increase in the number of mesangial cells, double contouring of the capillary loops found in specimens stained with silver salts. The most important ultrastructural feature here is the transposition of the mesangial cell processes on the loop perimeter between the endothelium and the basement membrane least marked in type II as well as the presence of subendothelial deposits (in type I) and subepithelial deposits (in type III). The definition of the location of deposits as either subendothelial or subepithelial cannot be achieved by histologic examination nor by immunofluorescence, but only by electron microscopy. Electron microscopy is particularly important for the diagnosis of type II, which is based on the appearance of a blackening of the lamina densa. This is possible only with electron microscopy. Regardless of possible further developments regarding the classification of this glomerulopathy (exclusion of type II and association of type I with type III), these finds are still of indisputable significance.

The basic feature of membranoproliferative glomerulonephritis, i.e. the transposition of mesangial cell processes, occurs also in other glomerular changes, for example in case of a rejection of a transplanted kidney and in the hemolytic-uremic syndrome [10–14].

Fibrillary glomerulonephritis

This glomerular disease can only be diagnosed by electron microscopy. It is characterized by the presence of fibrillar deposits measuring 18 to 20 nm. These deposits are found in the mesangial matrix and in the glomerular basement membranes [15–17].

Lupus nephritis

Ultrastructure examinations can be helpful also in the assessment of lupus-related changes.

Among other ultrastructural changes of sometimes essential diagnostic significance, the presence of so-called virus-like inclusions must be mentioned. This change occurs in glomerular endothelial cells and is caused by a deformation of the channels of the endoplasmic reticulum which is typical for lupus nephritis. This nephritis is accompanied by fingerprint-like deposits which are probably the result of changes in the DNA [18–23].

Thin basement membrane disease

Thin basement membrane disease, like minimal change disease, cannot be diagnosed by histologic examination. Sometimes the thinning of the basement membranes can be observed in specimens stained with the Jones' method, but this occurs extremely rarely. Also, this result does not provide sufficient basis for a definite diagnosis of this syndrome. For this, an assessment of the ultrastructure is absolutely necessary.

A thickness of maximum 250 nm of the lamina densa of the basement membrane has been assumed for the diagnosis of this syndrome. In addition, the change must involve the majority of the capillary loops [24–30].

Alport syndrome

In case of the Alport syndrome the light microscopy image can be diverse. The presence of immature glomeruli together with mature glomeruli and various glomerular changes, as well as the presence of interstitial cells with a foamy cytoplasm are considered as fairly characteristic. However, these changes appear also in other diseases and do not allow for a final diagnosis. Significant are, on the other hand, changes observed in electron microscopy consisting in an uneven thickness

of the basement membrane of the renal glomeruli and the characteristic splitting of the lamina densa. Other symptoms of this syndrome, apart from kidney disorders, such as hearing loss or ocular manifestations, do not always occur and usually appear late, and genetic analyses are performed very rarely. Electron microscopy is therefore decisive in these cases.

Structural changes of the lamina densa of the basement membrane are sometimes observed also in other glomerulopathies, for example in thin basement membrane disease. They are then, however, discrete, concern only small sections and consist in a thinning rather than a splitting of the structure [31–34].

Hemolytic-uremic syndrome

The light microscopy image of the hemolytic-uremic syndrome has no specific features, the glomerular changes are quite diverse: presence of thrombi, detachment of endothelial cells, double contouring of loop walls, loop wall thickening. Sometimes, these changes are indiscernible. The electron microscopy image is more characteristic. Apart from the transposition of the mesangial cell processes in the initial phase in the space created by the detachment of endothelial cells, it reveals the presence of a plasma-like matter. This matter encloses small fibrin fibers, fine myofibrils, platelets or platelet fragments, endothelial cells or endothelial cell fragments, detached mesangial cell processes. Detached endothelial cells retain some of their functions, such as the production of basement membrane. The mesangium shows changes called „netting", mesangiolysis and the presence of fibrin deposition. All these changes are identified above all by electron microscopy. They can persist for a certain time in recovering patients. In case of the occurrence of exponents of kidney damage in such patients a certain time after the acute symptoms have subsided, only the result of an electron microscopy can determine, if they are connected with the hemolytic-uremic syndrome or if they are symptoms of another glomerulopathy. This may involve difficulties with regard to the differentiation from the extremely rarely diagnosed fibrillary glomerulonephritis [35–38].

Focal segmental glomerulosclerosis

An important role is played by electron microscopy in detecting early changes, yet elusive in the light microscope. Here one should mention first of all, the early phase of glomerular sclerosis [39–42].

In recent years, the literature reveals little of the position concerning the importance of electron- microscopic study. Outweigh issues of immunology.

Some even say that the role of electron microscopy in pathomorphological practice is declining. Kidney pathology and in particular the pathomorphology of glomerulopathies represent a very strong argument against this view. Here, the value of electron microscopy cannot be overestimated. This is why pathomorphologists insist so strongly on securing biopsy material for such analyses.

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