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IgA nephropathy. Causes, symptoms and modern diagnostics of the most common glomerulonephritis

Nefropatia IgA – przyczyny, objawy i współczesna diagnostyka najczęstszego kłębuszkowego zapalenia nerek

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Summary

IgA nephropathy (IgAN) is the most common glomerulonephritis. Its causes are not fully understood and can be divided into genetic, environmental and infectious. The spectra of histopathologic and clinical course of IgAN are highly variable. Most patients remain asymptomatic for a long period of time and the first symptoms such as proteinuria, haematuria, and hypertension are not specific to IgAN. We do not know the definitive prognostic factors, so that we could precisely determine the IgAN progression, and consequently the risk of developing chronic and end-stage renal failure. Despite the knowledge progress, sensitive and specific diagnostic methods are still lacking. Although today renal biopsy remains the "gold standard" in the diagnosis of IgAN, the immunological, genetic, and proteomic diagnostics become more and more important. The proteomic analysis of proteins of low molecular weight made possible to carry out a differential diagnosis between healthy subjects and IgAN patients in remission of the disease, even in the absence of pathological proteinuria. Perhaps in the future it will be possible to develop the whole map of proteins to monitor different treatment regimens in IgAN.

Streszczenie

Nefropatia IgA (IgAN) jest najczęstszą wśród wszystkich glomerulopatii. Jej przyczyny nie są do końca znane i można je podzielić na genetyczne, środowiskowe i infekcyjne. Spektrum zmian histopatologicznych i przebieg kliniczny w IgAN są bardzo zmienne. U większości pacjentów rozpoczyna się i/lub przebiega bezobjawowo przez dłuższy czas, a pierwsze objawy jak białkomocz, krwinkomocz i nadciśnienie tętnicze nie są swoiste dla IgAN. Nie znamy również jednoznacznych czynników prognostycznych, dzięki którym moglibyśmy precyzyjnie określać ryzyko progresji IgAN, a w efekcie także przewlekłej i schyłkowej niewydolności nerek. Pomimo postępu wiedzy nadal brak jest czułych i specyficznych metod diagnostycznych. Do dnia dzisiejszego biopsja nerki pozostaje „złotym standardem" w diagnostyce IgAN, jednak coraz większego znaczenia nabiera diagnostyka immunologiczna, genetyczna i proteomiczna.

Analiza proteomiczna białek o niskiej masie cząsteczkowej umożliwia np. diagnostykę różnicową osób zdrowych oraz pacjentów z IgAN w okresie remisji choroby, czyli nawet w przypadku braku patologicznego białkomoczu. Być może w przyszłości będziemy mieli do dyspozycji całą mapę białek, tak aby monitorować dzięki temu różne schematy leczenia IgAN.

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INTRODUCTION

Chronic kidney diseases (CKD) belong to the twenty-first century civilization diseases (1). Due to the often long period of clinical latency, diagnosis of CKD is frequently performed at the stage of advanced renal damage. In the recent years, a number of epidemiological studies involving selected patients populations from North and South America, Australia, Asia and Europe

were published. Depending on the region the overall CKD prevalence ranges between 6 and 20% (2). In Poland, according to the POLNEF study, CKD was confirmed in 16% of population (3). Taking into account these data, the CKD incidence is a far greater problem than previously thought.

The most common cause of CKD is the damage and fibrosis of renal parenchyma second to diseases directly leading to it, and less often due to urinary outflow obstruction or vascular lesions. The most common diseases include diabetic nephropathy, hypertensive nephropathy, glomerulonephritis (GN), tubulointerstitial kidney disease and polycystic kidney degeneration (4).

GN are a heterogeneous group of diseases with different pathogenesis, for which the common denominator is inflammation (4). They represent second cause of renal replacement therapy, probably because the onset of the disease affects young and middle-aged people (5). Generally, GN are divided into primary and secondary (6). The latter develop in a consequence of another, ongoing disease processes, e.g. systemic vasculitis or lupus erythematosus (5).

IgA nephropathy (IgAN) was first described by the French pathologist Jean Berger in 1968. It is the most common GN and depending on the continent represents 15-40% of all biopsy-proven primary GN (7). Although the disease is associated primarily with the mesangial deposition of IgA and mesangial cells proliferation, the spectrum of histopathological and clinical course is highly variable (8). IgAN is most common in Asia and the Caucasus, more rare in Europe and the United States, and is diagnosed only occasionally in Africa. Indirectly, this may be associated with more aggressive diagnostic approach and more frequent renal biopsies, or perhaps with the diet (9). The largest number of cases is diagnosed in the second and third decades of life. Although most cases of IgAN develop *de novo*, there is also a familial disease pattern (10).

The IgAN causes are not completely understood. They can be divided into genetic, environmental and infectious factor groups. In genetically predisposed individuals, the presence of yet unknown triggering factors, initiates the deposition of immunoglobulin A (IgA) in the glomerular mesangium. This results in an inflammatory reaction, mesangial hypercellurality and the appearance of clinical symptoms. IgA presents two isoforms (IgA1 and IgA2), existing as a monomeric or polymeric (mostly dimeric) form (10). In the mesangium of IgAN patients mostly deposits of IgA1 polymers are present. Importantly, a defective glycosylation in the hinge region of the heavy immunoglobulin chain (absence of galactose) result in an increased serum concentration of IgA1 subclasses with deregulated molecular structure. It is believed that the immune complexes of high molecular weight, which form with the described IgA1 low-galactose subclasses, are responsible for mesangial proliferation, local release of inflammatory mediators and glomerular damage (11).

Thanks to the genetic studies in patients with familial or sporadic IgAN, several gene polymorphisms were identified that may play important roles in the development of IgAN. For example, polymorphisms of the major histocompatibility complex (MHC), including increased incidence of HLA-BW35, HLA-BW12 and HLA-DR4 were described (4).

The role of environmental factors, such as smoking, has been known for many years and has been confirmed in many IgAN studies. Overweight, obesity, lipid disorders and lack of physical activity were also identified as independent risk factors for CKD and increasing proteinuria in IgAN, although their effects vary between patients with different dynamics of the disease progression. It is known that IgAN may develop and exacerbate in response to the infectious diseases, particularly of the upper respiratory or gastrointestinal tracts. Cases of IgAN after preventive vaccinations, infections associated with tooth extraction or tonsillectomy were also reported. Additionally, IgA may deposit in the mesangium in the course of other diseases, such as liver cirrhosis, inflammatory bowel disease or ankylosing spondylitis (10).

Most of IgAN patients remain asymptomatic for a long time, and the first IgAN symptoms, such as proteinuria, haematuria, and hypertension are not specific (4). The color of urine is mostly brown, less frequently red and often described by the patients as a “tea color”. The time correlation to infection is also characteristic. The haematuria occurs typically 24-48 hours after onset of infection. This is an important clinical parameter differentiating IgAN from acute post-infectious glomerulonephritis, where the disease symptoms appear after 2-3 weeks. In most IgAN patients haematuria disappears spontaneously within a few days, although microscopic haematuria can persist. In most cases, over the next few year several episodes of haematuria can present, but these are seldom correlated with the stage of renal failure. On the other hand, asymptomatic haematuria, often associated with proteinuria is found in 30-40% of patients at routine laboratory tests (10). The nephrotic syndrome affects only about 5% of IgAN patients and is more common in children and teenagers. The nephrotic range proteinuria often coexists with glomerulosclerosis (10).

Despite the knowledge progress, the sensitive and specific methods to diagnose IgAN are lacking. The definitive prognostic factors remain unknown, so that we can not accurately determine the risk of IgAN progression to chronic and end-stage renal failure.

IgAN biochemical diagnostics is not different from the diagnostics used in other CKD. Special attention should be paid to the appropriate urine collection, and to all the factors that may affect the evaluation of daily proteinuria, e.g. urinary tract infections, menstrual bleeding or cancer. Determination of protein or albumin in the urine sample is a much better method than semi-quantitative strip tests, which are characterized by a high percentage of false positive and negative results (4).

To date, renal biopsy remains the "gold standard" in the diagnostics of IgAN. It is an important tool for both diagnosis and prognosis. IgAN Oxford classification, introduced in 2009, is currently in force. Its aim is to unify the histopathological diagnosis of renal biopsies throughout the world. Four variables included in the Oxford classification (i.e. mesangial hypercellurality, endocapillary hypercellurality, segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis) have been identified as the most correlated with the clinical picture of IgAN, i.e. the severity of hypertension, glomerular filtration rate reduction and proteinuria (12).

The immunological diagnostics is far from desired. The elevated levels of IgA in serum is found in 30-50% of patients with IgAN, but with no correlation to the disease activity or severity. Also, the increased levels of IgA1 immunoglobulin subclasses with deregulated molecular structure are neither sensitive nor specific enough to be used in clinical practice (13).

Many authors look for genes and their polymorphisms which could correlate with susceptibility to disease and could allow to predict the rate of IgAN progression. Lately, genome-wide association study (GWAS) was increasingly used to identify loci related to the increased risk of IgAN (14). Kiryluk et al. identified six novel genome-wide significant associations, 4 in ITGAM-ITGAX, VAV3 and CARD 9 and two independent signals HLA-DQB1 and DEFA (15). Another example would be an untranslated gene megsin region polymorphism, which is a serine protease inhibitor, and has been shown to be overexpressed in the mesangial cells of IgAN patients. This gene haplotypes 2093-2180 T and A23167G occurred in patients with rapid progression of the disease and more advanced histopathological changes (16). In turn, the loci identified in MHC are associated with a higher risk of IgAN (17). Attention has been paid also to deletions within the regulatory genes CFHR 1 and CFHR 3 on chromosome 3 and genes encoding TNF (18).

The proteomic studies are increasingly used in the clinical diagnostics of renal diseases. Firstly, because urine is a research material easy to obtain. Secondly, they allow to determine the qualitative and quantitative composition of the peptide-protein in urine, with the number of identified proteins of different weight and size, as well as fragments of DNA and RNA (19). To date, several databases were established, e.g. The Human Kidney and Urine Proteome Project and European Kidney and Urine Proteome, which are used in ureoproteom characteristics, namely assessing the profile of proteinuria. In the urine samples from IgAN patients an increased concentration of complement components, coagulation factors, extracellular matrix proteins, intracellular and transmembrane proteins were identified (20). Noteworthy is the fact that the proteomic analysis of proteins of low molecular weight made possible to carry out a differential diagnosis between healthy subjects and IgAN patients in remission of the disease, i.e. in the absence of pathological proteinuria. The analysis of urine proteins of low molecular weight allows also to distinguish patients with IgAN from healthy individuals, even when full remission and absence of pathological proteinuria (21). Perhaps in the future we will develop also the whole map of proteins, so that we can monitor multiple treatment regimens in IgAN. Rocchetti et al. provided evidence that urinary proteomics can predict IgAN treatment efficacy with angiotensin-converting-enzyme inhibitors (22).

CONCLUSIONS

The increasing use of modern immunological, genetic and proteomic diagnostic tests allows a better understanding of the IgAN pathophysiology and the identification of new biochemical pathways, which may be used in the future to make patient care more efficient and effective.

BIBLIOGRAPHY

1. Nowicki M: Metody wykrywania i oceny postępu przewlekłej choroby nerek. Choroby serca i naczyń 2007; 4(3): 137-141.
2. Król E, Rutkowski B: Przewlekła choroba nerek – klasyfikacja, epidemiologia i diagnostyka. Forum nefrologiczne 2006; 3: 13-17.
3. Czekalski S: Przewlekła choroba nerek – przewlekła niewydolność nerek w Polsce i na świecie. Przew Lek 2007; 1: 10-16.
4. Klinger M, Dziemianko I: Choroby nerek i dróg moczowych. Choroby kłębuszków nerkowych. [W:] Szczeklik A, Gajewski P (red.): Interna Szczeklika. Podręcznik chorób wewnętrznych. Wyd. VI, MP, Kraków 2014: 1403-1561.
5. Klinger M: Współczesna nefrologia – nowe metody, nowe leki i wciąż wiele trudnych wyzwań. Pol Arch Med Wewn 2007; 117: 35-41.
6. Klinger M, Mazanowsk O: Pierwotne kłębuszkowe zapalenie nerek – współczesny algorytm postępowania diagnostycznego i terapeutycznego. Pol Arch Med Wewn 2008; 118(10): 567-571.
7. Le W, Liang S, Hu Y et al.: Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinease adult population. Nephrol Dial Transplant 2012; 27: 1479-1485.
8. Barbour SJ, Reich HN: Risc stratification of patients with IgA nephropathy. Nephrol Dial Transplant 2003; 18: 1541-1548.
9. Wada T, Nakao T, Matsumoto H et al.: Relationship between dietary protein intake and the changes in creatinine clearance and glomerular cross-sectional area in patients with IgA nephropathy. Clin Exp Nephrol 2015; 19(4): 661-668.
10. Baratt J, Feehally J: Immunoglobulin A Nephropaty and Related Disorders. [In:] Gilbert S, Weiner ED (eds.): National Kidney Foundation's. Primer on kidney disease. 6th edition. Elsevier Saunders, Philadelphia 2014: 185-197.
11. Barratt J, Feehally J: Primary IgA nephropathy: new insights into pathogenesis. Semin Nephrol 2011; 31: 349-360.
12. Herzenberg AM, Fogo AB, Reich HN et al.: Validation of the Oxford classification of IgA nephropathy. Kidney Int 2011; 80: 310-317.
13. Barratt J, Smith AC, Feehally J: The pathogenic role of IgA1 O-linked glycosylation in the pathogenesis of IgA nephropathy. Nephrology (Carlton) 2007; 12: 275-284.
14. Foo JN, Liu J, Yu XQ: GWAS reveal novel IgA nephropathy risk loci. Oncotarget 2015; 6(18): 15738-15739.
15. Kiryluk K, Li Y, Scolari F et al.: Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet 2014; 46(11): 1187-1197.
16. Li YJ, Du Y, Li CX et al.: Family-based association study showing that immunoglobulin A nephropathy is associated with the polymorphism 2093C and 2180T in the 3'untranslated region of the Megsin gene. J Am Soc Nephrol 2004; 15: 1739-1743.

17. Gharavi AG, Kiryluk K, Choi M et al.: Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet 2011; 43: 321-327.
18. Freda B, Barden G: How Benign Is IgA Nephropaty with Minimal Proteinuria. J Am Soc Nephrol 2012; 23: 1607-1610.
19. Niemczyk M, Pączek L: Proteomika w nefrologii klinicznej. Nephrol Dial Pol 2010; 14: 31-33.
20. Mucha K, Bakun M, Jaźwiec R et al.: Complement components, proteolysis-related, and cell communication-related proteins detected in urine proteomics are associated with IgA nephropathy. Pol Arch Med Wew 2014; 124(7-8): 380-386.
21. Julian BA, Wittke S, Haubitz M et al.: Urinary biomarkers of IgA nephropathy and other IgA-associated renal diseases. World J Urol 2007; 25(5): 467-476.
22. Rocchetti MT, Centra M, Papale M et al.: Urine protein profile of IgA nephropathy patients may predict response to ACE-inhibitor therapy. Proteomics 2008; 8(1): 206-216.

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